ANNALS of ALLERGY

Published by
The American College of Allergists

Volume 19 July, 1961 Number 7

PARTICLE SIZE PRODUCED BY VARIOUS INSTRUMENTS FOR INHALATION THERAPY

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INHALATION therapy has a long history of use in the treatment of diseases of the respiratory tract. Measures used have ranged from the inhalations of fumes from burning nitre paper[1] to the rather coarse medicinal sprays delivered by "atomizers." In the presence of bronchospastic conditions, as exemplified by bronchial asthma and chronic bronchitis, a special problem exists. Here, the inhalation of vasoconstrictors and bronchodilators is indicated, not for the purpose of reaching the enormous absorptive surface of the alveoli of the lungs, but for their local effects on the fine bronchioles. For this reason, a rather narrow range of particle size is indicated.

This is relatively less important where the desired therapeutic effect is achieved essentially through systemic action, as with medication designed for the treatment of headaches (the ergotamine derivatives) or with antibiotic therapy.

The limitations in particle size of medication intended for local bronchodilator effect are dictated by the requirement that the maximum possible amount of drug reach the finest ramifications of the bronchiolar tree. Various investigators have considered the idea that a particle size of 1.0 to 3.0 microns is optimal, with as few particles as possible outside this range.[2-4] "Nebulizers which produce particles of 1.0 *u* or less are not as satisfactory since much of the mist either passes into the alveoli and is absorbed or is lost in expiration with little deposition on the bronchial mucous membrane."[4] The ultra-fine mists described by La Mer and his associates[5,6] are, therefore, not suitable for bronchiolar deposition.

Particles substantially larger than 3 microns in diameter present a number of disadvantages. In conformity with Stokes' law, they tend to have a rapid rate of fall, modified by turbulence in the respiratory tract. Hence, they are

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likely to be deposited in the oropharynx and upper respiratory tract. Furthermore, those that reach the bronchi tend to be trapped in the larger branches and fail to reach the bronchioles where they would be maximally effective.[2]

In the case of drugs intended for purely local effect, such as mucolytic agents, this represents wasted medication. When drugs are absorbed through the mucous membranes, there will still be some indirect pharmacological activity on the bronchioles by means of the blood stream, but the likelihood of systemic side effects is increased. This is particularly true in the case of the bronchodilators evaluated in the present study, where their action through the blood stream may result in a higher cardiac to pulmonary ratio of effect.

Apart from the waste or increased systemic side effects, it may be harmful to have excessive amounts of medication deposited in the oropharynx. Some drugs used in pulmonary therapy have local astringent or irritative effects, while others leave an unpleasant aftertaste which might discourage the use of the prescribed medication. Specifically, the bronchodilators under study may produce dryness of the throat and tracheal and bronchial irritation.

Even when only a small proportion of the droplets are large, there may be an appreciable incidence of such side effects. Simple calculation reveals that a ten-fold increase in the diameter of a droplet represents a thousand-fold increase in mass. It can easily be seen, therefore, that if one droplet in ten is larger by this factor, then 99 per cent of the material is accounted for by these larger particles. Consequently, the apparatus employed to produce the mist should be capable of delivering a fine, uniform cloud of droplets of the indicated therapeutic agent.

DETERMINATION OF PARTICLE* SIZE

The problem of collecting and measuring aerosol droplets has been investigated by many experimenters. Depending on the methods, materials and criteria used, the various published results have differed by factors of 2, 5, 10 and even 20 times.[3,5-9]

The disparity can occur in only a few places:

1. Variations in the instruments used to produce the particles.
2. Variations in the method of collecting the particles.
3. Errors in measurements or calculations.

If it is assumed that the nebulizers from any one manufacturer are uniform, there remain the questions of air pressure, saturation or degree of humidity in the air, and composition of the fluid vehicle used in the determinations.

The collecting material may be air; i.e., determination of particle size by measurement of the rate of fall. Or, it may be a surface sensitized to respond to the droplets by a change in color, change in appearance, or change in density of a surface, or by entrapment in a fluid.

*The term particle is used to describe both droplets and dry particles. Droplet is used where the medication is usually dispersed in the liquid phase.

Some investigators have used a fixed air pressure to actuate the nebulizer, and have varied the air pressure to study the effect on the volume and size of the droplets. Apparently, any increase in pressure above one atmosphere has little influence on the mean droplet size.[8,9]

PLAN OF STUDY

After reviewing the problem and the work of other investigators, the following plan was adopted.

A moderately air-tight plastic box was constructed with a porthole to permit entry of the nebulizer tip and a means of producing approximately 100 per cent relative humidity. This was fitted with a holder that permitted prepared microscope slides to be held in either of two fixed positions, as required, and a means for covering these slides with plastic protectors to avoid particle collection except as desired (Fig. 1).

The basis of the approach was a simulation of clinical conditions, accurately standardized for reproducible results.

INSTRUMENTS TESTED

It is of interest to distinguish between sprays, atomizers and nebulizers. A *spray* is any instrument from which droplets are dispersed into the air. Usually these particles are coarse, but their size depends upon the nozzle characteristics and pressure. An *atomizer* is a specific type of spray which depends upon the Venturi effect of a jet of gas passing across the tip of capillary tube dipping into a solution. A *nebulizer* is a specialized atomizer delivering fine droplets within a limited range from a chamber, with the coarser droplets removed by impingement.

The following instruments, widely used for inhalation therapy, were studied:

1. Vaponefrin standard glass nebulizer, (2 units).
2. Vaponefrin standard plastic nebulizer.
3. Vaponefrin pocket-size plastic nebulizer.
4. DeVilbiss all glass nebulizer No. 40, (2 units).
5. Isuprel Mistometer (pressure container).
6. Medihaler-Epi (pressure container).

In the first four instruments, the solution used was Vaponefrin Solution, containing 2.25 per cent racemic epinephrine and 7.5 per cent glycerine. It has a viscosity of 1.21 centipoises at 20° C, specific gravity of 1.0360 at 25° C, and a surface tension of 68.9 dynes/cm^2 at 21° C. Since the same solution is used in all four instruments, the experiment furnishes a valid comparison of the instruments themselves. It may be noted that instruments 1, 2 and 3 employ a spherical baffle to break up and divert the larger droplets, while instrument 4 depends on a curved nozzle and turbulence to remove the larger droplets, which impinge on and adhere to the walls of the vessel.

Instrument 5 is equipped with a vial containing 0.25 per cent isoproterenol hydrochloride solution in 33.25 per cent ethanol and fluorohydrocarbon propellant. Instrument 6 contains 7.0 mg of micronized epinephrine bitartrate

per cc of fluorohydrocarbon propellant; its medication is released as dry particles. Both of the latter instruments operate by means of metered valves to release a measured amount of material with each pressure on the vial.

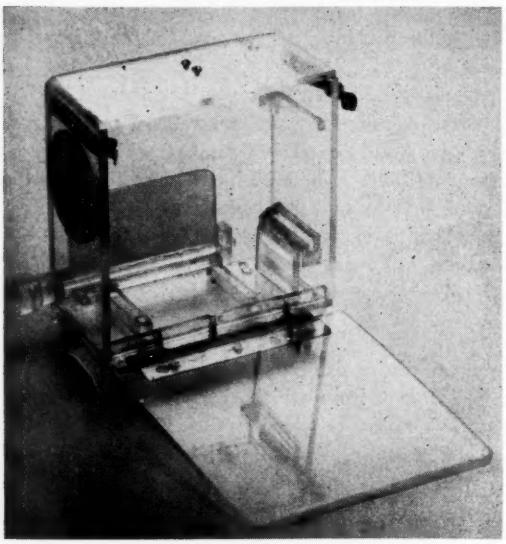

Fig. 1. Device for exposure of prepared slides to vapor from nebulizers at 100 per cent relative humidity.

The last two cannot be considered true nebulizers since the active ingredient is dissolved or suspended in the propellant and the particle size is produced by the explosive release of the propellant and not by true nebulization.

COLLECTION

Great variation in the size of the droplet—or its residue—can be expected if the humidity of the surrounding air and its temperature are permitted to vary. Because evaporation increases rapidly with diminishing size of the droplets, it is important that the humidity be maintained at a level slightly over 100 per cent. This is achieved by evaporating de-ionized water to achieve saturation and then injecting the substance to be tested. Since the latter contains solutes, its vapor pressure is lower than that of pure water, and the atmosphere will be supersaturated with respect to the test substance. The condition of high humidity also has the advantage that it closely resembles the environment of the mouth and bronchi.

The plastic collection chamber was built with a rack to hold a single microscope slide directly opposite the nebulizer outlet. Another rack was built into the base of the unit to hold a slide horizontally. Plastic plates controlled from outside the chamber were so designed that they could be made

to cover a slide and thus prevent droplets from reaching it, or turned aside to permit droplet collection.

Experiments showed that we could not expect a uniform distribution of droplets all over approximately 1 x 2 inches of the surface of the microscope slide. The inability of dry surfaces to collect droplets of the order of ½ to 1 micron precluded their use. Tests with various oils showed that Shillaber's Light Microscope Immersion Oil has a low surface tension and a low absorption capacity for moisture, could collect particles as small as ½ to 1 micron as well as larger ones, and could prevent evaporation of the droplets for ten to fifteen minutes. Other oils were found to have too high a surface tension, or to contain organic material which resulted in absorption of water from the smaller droplets.

The oil film on the slide was prepared by covering the surface with the oil in a dust-free environment and permitting the oil to run off by holding the slide in a vertical position. The excess oil at the bottom was wiped off with lens paper. The thickness of the resulting oil film was found to be approximately 0.1 mm. An alternative method is to spread three drops of the oil with a glass rod over an area of 25 x 50 mm of slide and permit it to flatten for three minutes.

The time of exposure of the prepared slide in the aerosol chamber is of great importance, as is the method of exposure. The first testing was done with a coated microscope slide held vertically, three inches from the nebulizer outlet. This was found to have serious mechanical disadvantages including some oil being blown off the slide by the pressure-container type of instrument. This method was abandoned, even after several improvements, in preference to the horizontal slide under controlled timing. Since the largest particles fall most rapidly, the longer the exposure, the greater the number of small particles.

The following method was adopted: After the chamber became saturated with water vapor, the outlet of the nebulizer was inserted through a port in the collection chamber (Fig. 2). The ambient temperature was controlled to $\pm$ 0.25° C.

To produce the mist, the instruments were actuated* five times in rapid succession, with the slide covered. The covering plastic was then rotated out of the way, and the instrument operated twice more. A timer was started, and at the end of five minutes the slide was removed and immediately put under the microscope. The latter was set for fixed conditions of 25X objective and 10X eyepiece, with an eyepiece reticle inset with spacing of 0.37 units to the micron. The examiner then made a count in ten fields on the slide.

Two experimenters participated in this study. Each gave the rubber bulbs of the Vaponefrin and DeVilbiss nebulizers a "firm, sharp squeeze," but since the experimenters differed in muscular strength, this introduced a variable. Comparison of their findings showed only unsystematic minor

*By squeezing the bulb on the nebulizer or pressing the metered valve on the pressure container.

variations; hence, their results were averaged. In clinical practice, such variations are bound to occur, and an average result appears valid, providing extreme deviations do not occur. The Medihaler and Mistometer units produced standard sprays, dependent on the uniformity of the propellant pressure and the metering valve; hence the problem of deviation did not arise in their cases, unless the valve was incompletely depressed.

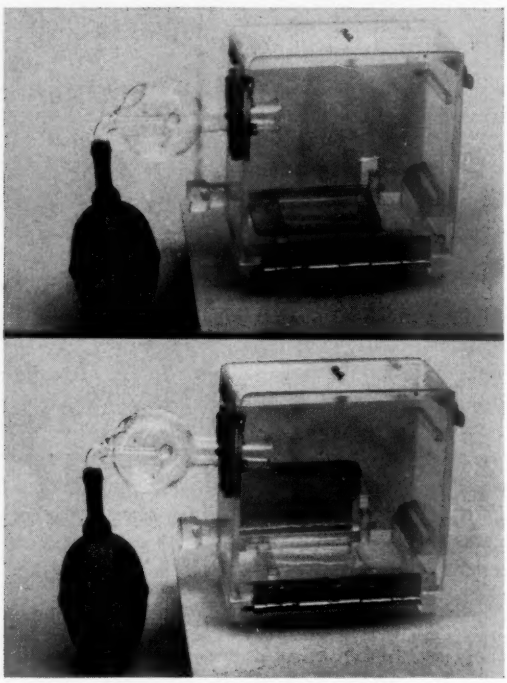

Fig. 2. Vaponefrin standard glass nebulizer in position for droplet collection. *(Upper photo)* Plastic protective plate down to protect collection slide. *(Lower photo)* Plate raised out of way to permit droplet collection.

SAMPLING

Chance variations and varying depth of the oil coating precluded a perfectly even distribution of particles over the entire surface of the slide. An area was selected at random and used if the number of droplets were deemed sufficient and representative. After four areas had been selected for photography and ten areas for visual measurement, a slide was scanned once more to look for any odd groupings of very large or very small particles.

MEASUREMENT

Photographic.—A uniform photomicrographic system was set up. A Bausch & Lomb stage micrometer was photographed under the same condi-

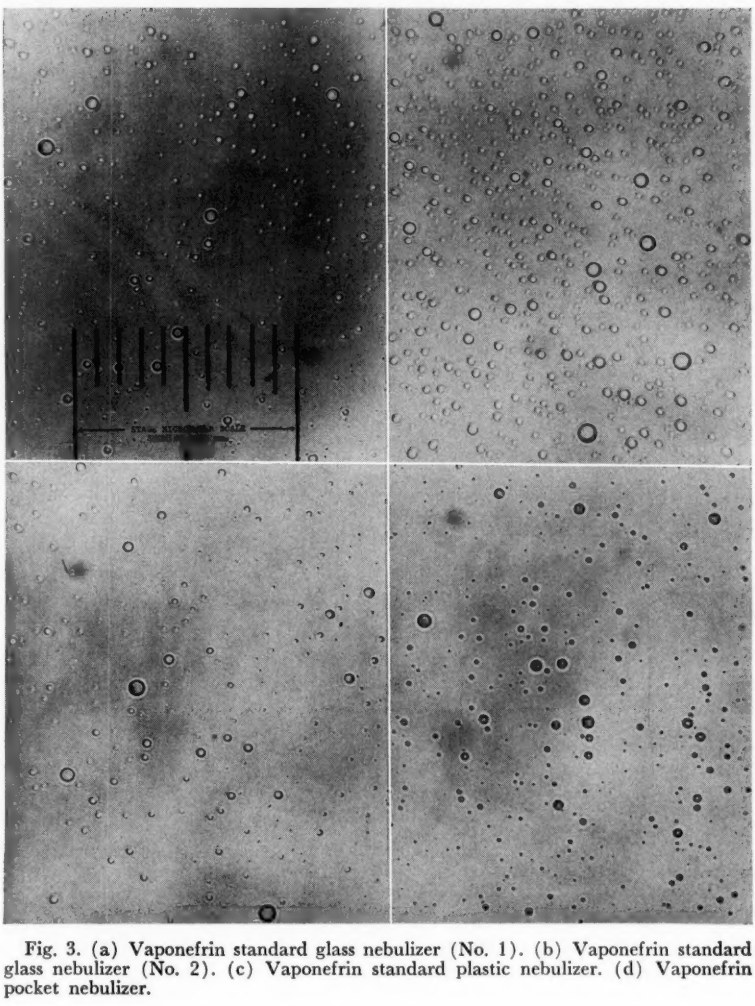

Fig. 3. (a) Vaponefrin standard glass nebulizer (No. 1). (b) Vaponefrin standard glass nebulizer (No. 2). (c) Vaponefrin standard plastic nebulizer. (d) Vaponefrin pocket nebulizer.

tions and used as the measuring device to determine the size of the photographed particles. A final magnification of 1000 X was adopted as the best compromise which would resolve ½ micron droplets while preserving an adequate field. Visual examination had shown this to be a satisfactory minimum size. Since the particles were floating in oil, exposures were made at 1/4000 second to stop motion. The depth of focus and contrast were increased to the maximum by stopping down the microscope condenser to the point at which diffraction rings began to appear around the droplets. Phase microscopy could not be used because the narrow zone of sharp focus would

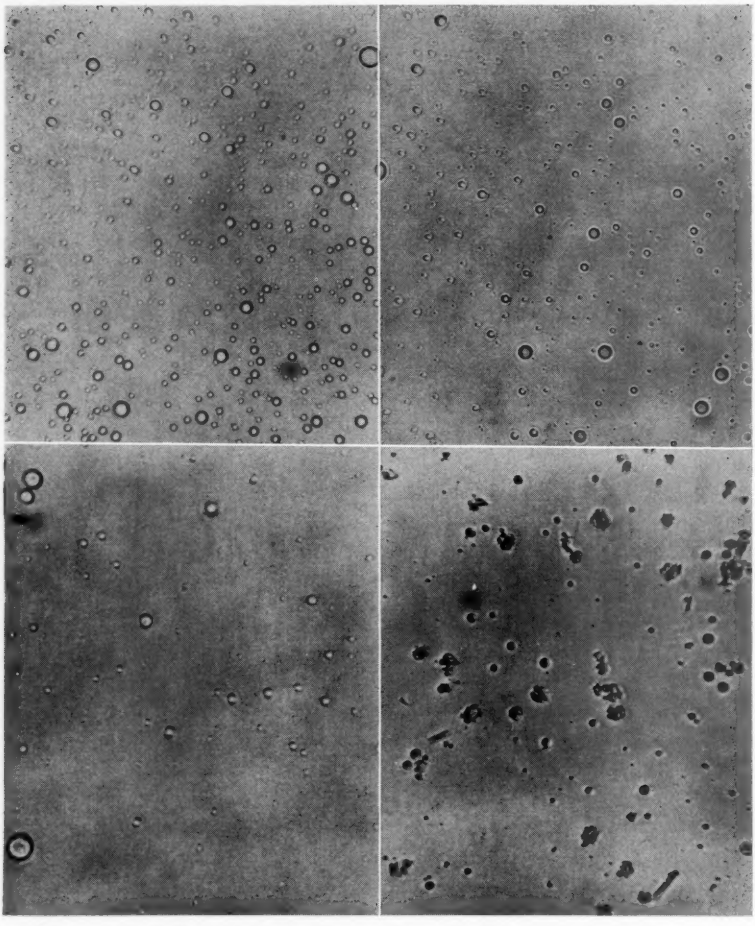

Fig. 3. (e) DeVilbiss No. 40 nebulizer (No. 1). (f) DeVilbiss No. 40 nebulizer (No. 2). (g) Isuprel Mistometer. (h) Medihaler-Epi.

make photographic measurement inaccurate. The diameters seen would depend on the vertical location of the plane of focus compared with the true diameter of the droplets. All measurements were made on the finished prints by one technician and checked by another.

Visual.—A field was selected under the microscope and the particles were measured as they drifted under the eyepiece reticle. A sufficient number of fields was selected to total 200 particles. The whole slide was then scanned and a separate count made to determine the ratio of large particles to small ones.

Errors.—The greatest accuracy was obtained for those particles which were closest to the best fit between lines. Since there were thirty-seven lines in the eyepiece micrometer to 0.01 mm on the stage micrometer, or 3.7 lines to each micron, the visual measurements clustered about 2.7 micron intervals. The photographic measurements were made with a 1 micron ruler, and therefore clustered about ½ and 1 micron intervals. At these magnifications, a liquid droplet floating in a liquid presents no sharp photographic boundaries. The photographic and visual measurements were consistent within the limits of experimental error.

RESULTS AND INTERPRETATION

The photographs were taken under conditions that showed the edges of the droplets as black rings. Although more difficult to perform, the visual observations were sharper than the photographic, especially in the submicron range. The photographic focus was more responsive to droplets of one circumference since it had to be set for one depth, whereas the visual focus could be varied.

Figure 3 (a to h) shows typical photographic results obtained with various instruments, using the solutions appropriate to their clinical application. Figure 4 (a to h) presents graphs showing particle size distributions for the various instruments. The black bars give the visual readings and the gray bars the photographic measurements.

Our conclusion regarding the dependability of the scoring would definitely favor the visual readings up to one micron diameter, and the photographic measurements over one micron. Many of the submicron particles did not register well enough photographically to be counted.

TABLE I. PARTICLE SIZE AND DISTRIBUTION

Instrument	Average Size of Particles		Per Cent 3u or Smaller		
	Photo	Visual	Photo	Visual	Average
Vaponefrin standard glass (unit 1)	1.74	1.61	87%	94%	90.5%
Vaponefrin standard glass (unit 2)	1.96	2.01	82%	88%	85%
Vaponefrin plastic	1.88	1.95	90%	83%	86.5%
Vaponefrin pocket size	2.17	1.78	74%	88%	81%
DeVilbiss No. 40 (unit 1)	1.92	1.81	85%	87%	86%
DeVilbiss No. 40 (unit 2)	2.11	1.46	80%	88%	84%
Medihaler—Epi	3.06	3.62	61%	67%	64%
Isuprel Mistometer	3.33	3.7	41%	61%	51%

(Also: Figure 3 and Figure 4, with keys to the data)

Study of the graphs shows close correspondence of the four Vaponefrin nebulizers and the two DeVilbiss units. The Medihaler and Isuprel Mistometer were significantly less efficient in maintaining particle size within the optimum range. Table I provides a summary of the findings with respect to particle size and distribution for the various instruments and solutions.

It is believed that the shape of the measurement curve is more important and more accurate than the individual measurements and indicates the most

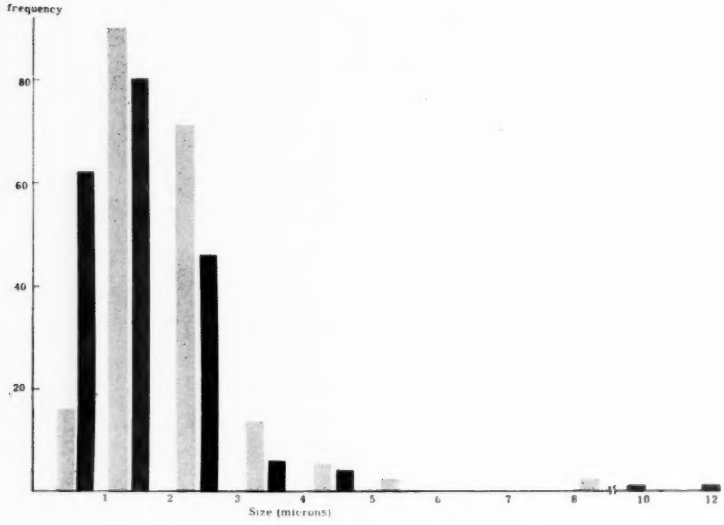

Fig. 4a.

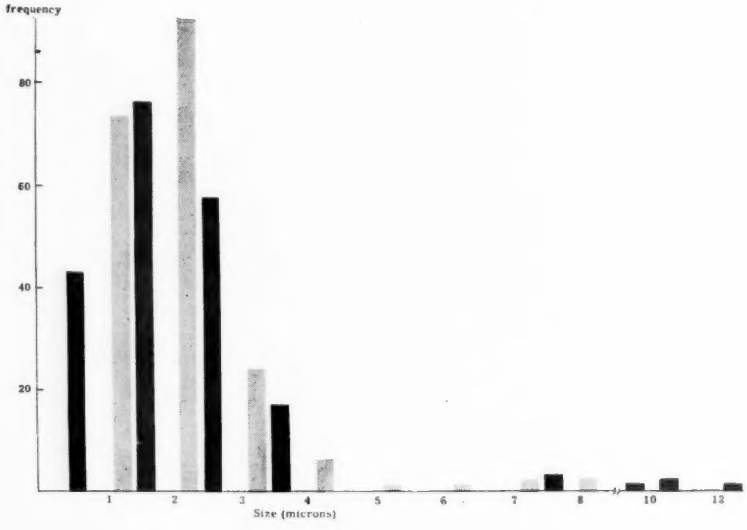

Fig. 4b.

Fig. 4. (a) Vaponefrin standard glass nebulizer (No. 1). (b) Vaponefrin standard glass nebulizer (No. 2).

In Figure 4 (a through h), black bars show frequency of droplets measured on photographs, and grey bars show frequency of droplets measured through the microscope.

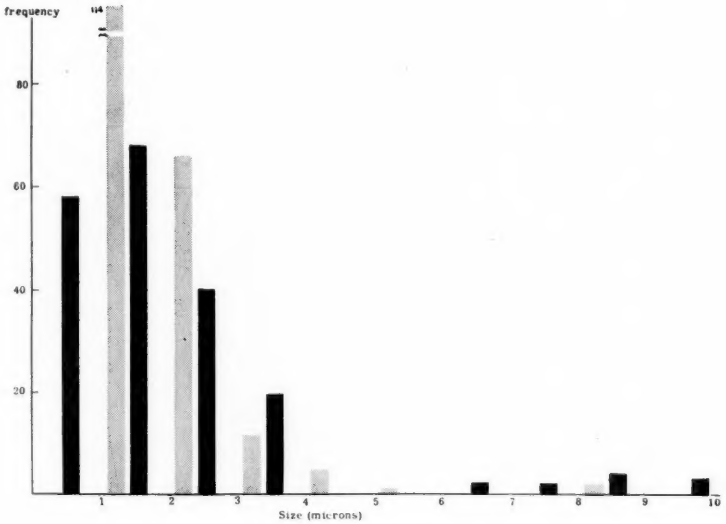

Fig. 4c.

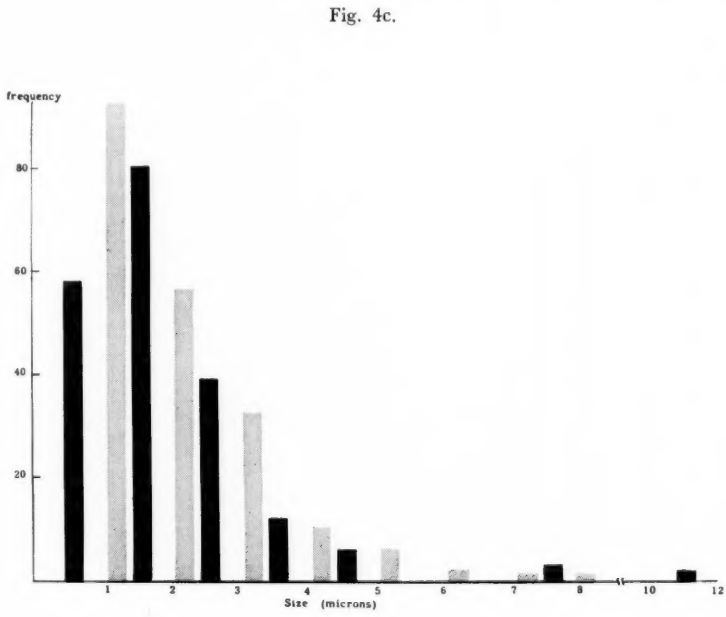

Fig. 4d.

Fig. 4. (c) Vaponefrin standard plastic nebulizer. (d) Vaponefrin pocket nebulizer.

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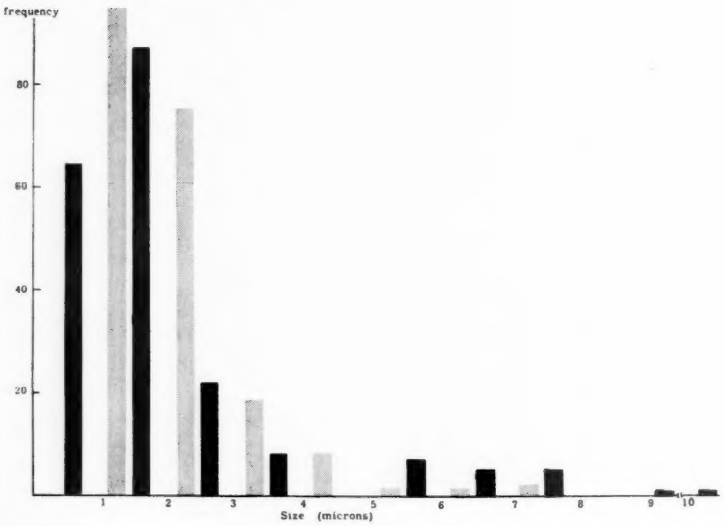

Fig. 4e.

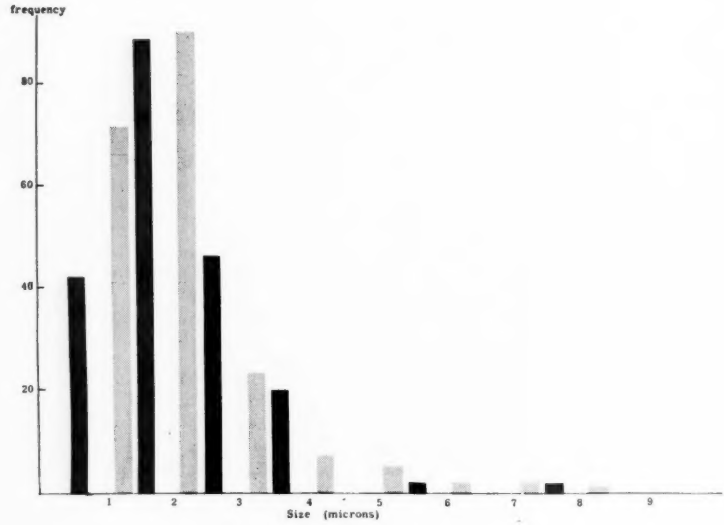

Fig. 4f.

Fig. 4 (e) DeVilbiss No. 40 nebulizer (No. 1). (f) DeVilbiss No. 40 nebulizer (No. 2).

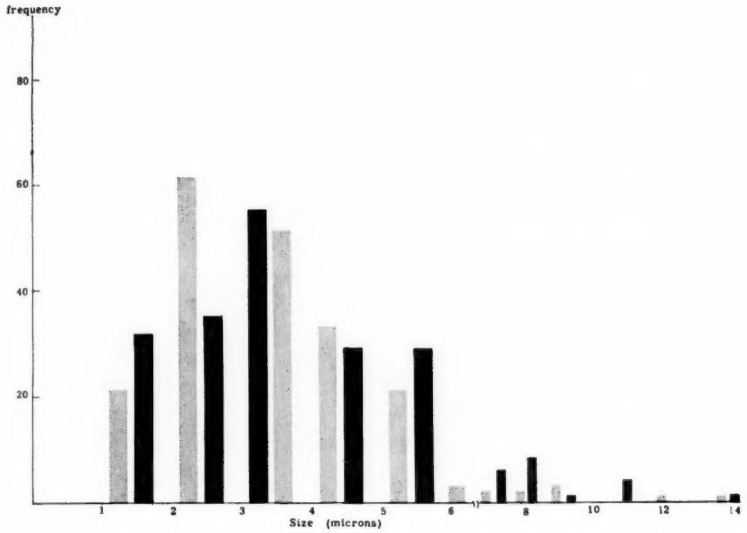

Fig. 4g.

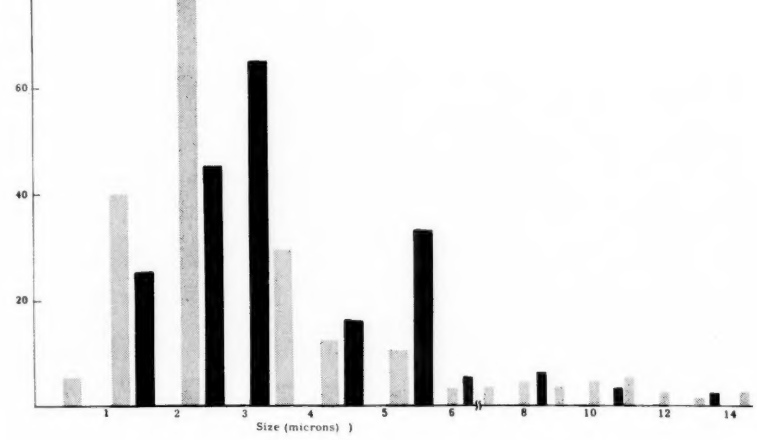

Fig. 4h.

Fig. 4. (g) Isuprel Mistometer. (h) Medihaler-Epi.

important features: the center of size distribution, the concentration of particles within the physiologic size limits, and the waste due to overlarge particles. The possibility of waste due to excessively small droplets could not be demonstrated in this study, but is negligible because of their small volume.

The clinical literature we have studied confirms the observation that 3 microns is the maximum size of particles which can readily penetrate to the terminal bronchioles.[2,4,7,8] Since it is essential that the medication be able to reach the terminal bronchiole, the size of the particle and its success in remaining suspended in the inspired air until it reaches its destination is important if the drug effect is to be exerted at the local level.

A final consideration of "real" versus "test" conditions is the problem of evaporation. After all the measurements are carefully made, some evaporation undoubtedly occurs between the outlet of the nebulizer (especially if held away from the mouth) and the high humidity of the bronchi. This evaporation would result in smaller particles, which should increase the ability of the aerosol solution to penetrate to the terminal bronchiole.

SUMMARY

A method for measuring the size and distribution of particles produced by various instruments for inhalation therapy is described. This employs both visual and photographic measurements.

Using the clinical criterion of production of droplets 3 microns in diameter or smaller, relatively efficient nebulization was produced by various Vaponefrin and DeVilbiss nebulizers. Other instruments tested were less efficient in this respect.

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CLINICAL ASPECTS AND TYPES OF DRUG-INDUCED PHOTOSENSITIVITY

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PHYSICAL ALLERGY is an intriguing subject. The layman finds it difficult to believe that true allergic reactions can occur as a result of exposure to purely physical elements, such as heat, cold, and light. The fact that such phenomena occur has been firmly established by numerous investigators and by a variety of techniques. Photosensitivity is the most common physical allergy known and it may be induced through several mechanisms; i.e., a metabolic disturbance (porphyria), a vitamin-deficiency state (pellagra), a systemic disease (lupus erythematosus), idiopathic phenomena (polymorphic light sensitive eruptions, solar urticaria), or exposure to a photosensitizing agent (drugs, certain plants, et cetera).

Drug-induced photosensitivity is becoming an increasing problem since many of the relatively new and quite useful therapeutic agents are capable of causing photosensitivity reactions. Among the more noteworthy reasonably new drugs that are known to produce photosensitivity reactions are the following: phenothiazines (Thorazine, Sparine, Compazine, Phenergan, Temaril, Pacatal, and many others), chlorothiazides (Diuril and Hydrodiuril), sulfonylurea derivatives (Orinase, Diabinese), and certain new antibiotics, such as demethylchlortetracycline (Declomycin), and the antifungal antibiotic, griseofulvin (Grifulvin and Fulvicin). Almost every sulfonamide derivative is capable of producing photosensitivity, and there are innumerable sulfonamides in use today. A drug, 8-methoxypsoralen (Methoxsalen), is currently being used to treat vitiligo because of its photosensitizing property. When one looks at this partial list of drugs and realizes how widely and extensively they are employed, it is easy to understand why drug-induced photosensitivity is becoming an increasing problem.

In addition to being photosensitizers, many of these compounds can produce contact epidermal sensitization. Occasionally, such contact sensitization is associated with photosensitization, and the role of sunlight in perpetuating the dermatosis should be recognized and dealt with appropriately. This phenomenon is seen most frequently among medical personnel handling phenothiazine derivatives and in workers who are using phenothiazines as insecticides.

Presented at the Seventeenth Annual Congress of The American College of Allergists, March 17, 1961, Statler-Hilton Hotel, Dallas, Texas.

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MECHANISM OF PHOTOSENSITIVITY

The term "photosensitization", when used in its broadest sense, means any of the unexpected changes which occur as a result of exposure to light, whether sunlight or artificial light, and the term "photosensitizer" can be

Fig. 1. *(left)* Acute eczematous eruption with a phenothiazine derivative being the photosensitizer.

Fig. 2. *(right)* Same patient as in Figure 1, illustrating normal skin in the unexposed area under the chin.

applied to the drug or agent which is responsible for inducing such a reaction. Photosensitivity may be divided into phototoxic and photoallergic sensitivity. In a phototoxic reaction, a molecule is activated by light and this results in a product which is toxic to the skin. The phototoxic process requires a photosensitizing agent in addition to an adequate amount of light of the proper wave length. This process will occur in all or almost all individuals who receive the challenge. In a photoallergic reaction, a true allergic mechanism is demonstrable. By definition, this type of phenomenon must have characteristics which fulfill the well-established criteria for an allergic type of reaction.

Baer and Harber[1] listed six points for distinguishing between phototoxic and photoallergic drug reactions:

1. Photoallergic reactions occur only in a small percentage of those persons exposed to the drug and sunlight, while phototoxic reactions can be elicited in all or many of those similarly exposed.

2. A phototoxic drug reaction can occur upon the first combined exposure to the drug and radiant energy, while a photoallergic drug reaction can occur only after an incubation period of sensitization.

3. A phototoxic drug reaction usually has the appearance of an intensified sunburn reaction. A photoallergic drug reaction also may closely resemble a sunburn reaction, but clinically and histologically, it often resembles other forms of cutaneous reactions known to be associated with allergic reactions.

4. In many cases of photoallergic drug reaction, a positive photopatch

test or photo drug test which has the characteristics of an allergic reaction can be elicited.

5. In photoallergic drug reactions, flare-ups may occur at unexposed sites distant from the site of light exposure.

6. In photoallergic drug reactions, the phenomenon of photo cross-sensitization to immunochemically related allergens may be demonstrated.

In many instances it is quite difficult to differentiate clinically between drug-induced phototoxic and photoallergic reactions without carefully

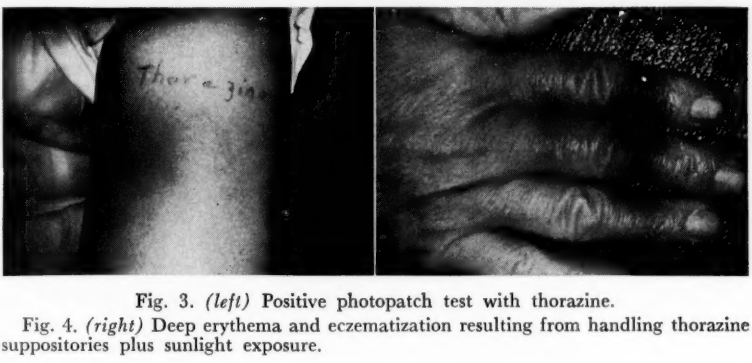

Fig. 3. *(left)* Positive photopatch test with thorazine.
Fig. 4. *(right)* Deep erythema and eczematization resulting from handling thorazine suppositories plus sunlight exposure.

performed investigative studies. Many, if not most, photosensitizing therapeutic agents are capable of causing both phototoxic and photosensitivity eruptions. The allergic response requires previous exposure and a sufficient lapse of time to allow the individual to develop an altered state of reactivity. A lesser amount of exposure is necessary to evoke an allergic response, but it may not appear as promptly as a phototoxic response. The phototoxic reaction is essentially an exaggerated sunburn response; whereas, the photoallergic response may produce a variety of types of lesions.

CLINICAL ASPECTS IN DETAIL

Clinically, it is usually not difficult to recognize a photosensitivity reaction, for the lesions are almost invariably erythematous and limited to light exposure areas. Many different types of reaction patterns can occur. The eruption may imitate other dermatological diseases, including contact dermatitis, seborrheic dermatitis, neurodermatitis, erythema perstans, erythema multiforme, pemphigus erythematoids, eczema of various types and lupus erythematosus. Any time skin lesions are limited to, or are predominantly located on, light exposed areas, the clinician should have a high index of suspicion for photosensitivity. When questioned, the patient will usually state that sunlight appears to make the disease worse, although some patients will not have noticed the sunlight factor. A careful drug history is then mandatory. At this point it should be emphasized that many photo-

sensitivity reactions do not have a demonstrable cause, and many such eruptions remain idiopathic in origin.

The scalp, upper eyelids and skin immediately under the chin are rarely involved in photosensitivity eruptions, and this can be an important point

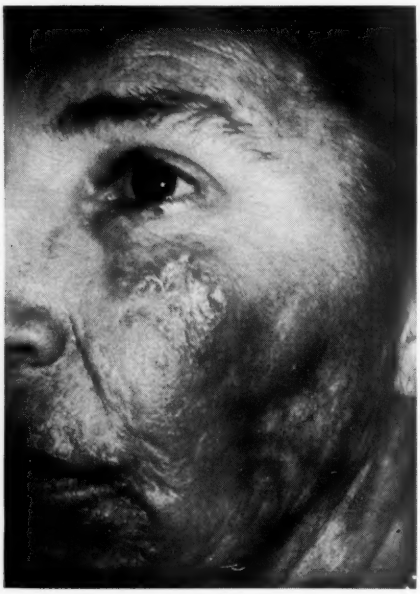

Fig. 5. This patient illustrates the atrophy and scarring that usually accompanies discoid lupus erythematosus.

in differential diagnosis. When lesions are on the arms, the lateral surface is almost invariably more involved than the medial surfaces. Cubital fossae are frequently spared, and this is unusual for most of the diseases that would be under consideration in differential diagnosis. If sunlight exposures occur predominantly while driving an automobile, the left side of the face and the left arm are more severely involved than the right. Fluorescent lighting can be the source of exposure; this possibility should, therefore, be discussed with the patient while investigating various situations of exposure. Photoskin tests can be a valuable aid in confirming the clinical diagnosis if appropriate equipment is available. Jillson and Curwen have developed a photoskin testing technique that utilizes a relatively inexpensive instrument.[2]

Prompt and proper treatment usually brings gratifying results. Whenever possible, the photosensitizing agent should be withdrawn and the patient should be informed as to the necessity of avoiding even minor exposures to sunlight. With extensive and severe eruptions, corticosteroid hormones

may be indicated; however, the antimalarial drugs (Aralen, Triquin, Atabrine, Plaquenil, Camoquin), plus appropriate topical medications such as a steroid cream or lotion, will often bring prompt improvement. After the acute episode has subsided, topical sunscreens are usually indicated. Five to ten per cent concentrations of para-aminobenzoic acid or a benzophenone derivative are excellent sunscreens.[3] It is frequently advisable to give the patient a list of related drugs that might also produce photosensitivity, and this list is particularly important when sulfonamides or phenothiazines are involved.

DISCUSSION

Following the initial observation at the turn of the century by Prime[4] that a drug (eosin) produced erythema on exposed surfaces, a gradually increasing body of knowledge relating to photosensitivity has accumulated. Blum and Pace,[5] in 1937, and Epstein,[6] in 1939, contributed their observations on porphyrins and sulfonamides. These presentations added significantly to the interest in photosensitivity phenomena. A large number of papers have been written on the subject of photosensitivity, and it is not the intent or purpose of this presentation to review the vast literature available. For those particularly interested in this subject, Sams[7] has recently published an excellent discussion on photosensitizing therapeutic agents. Among the more noteworthy recent studies of drug-induced photosensitivity are those of Cahn and Levy,[8] Epstein et al,[9] Epstein and Rowe,[10] Harber et al,[11] and Cloud et al.[12]

With the ever-increasing number of new drugs, including modifications of the structure of currently used therapeutic agents, the incidence of drug-induced photosensitivity will probably increase instead of decrease. Physicians should constantly remain aware of the fact that photosensitivity might be the source of an otherwise non-diagnosable eruption.

SUMMARY

Drug-induced photosensitivity is becoming an increasing problem because many of the relatively new and quite useful therapeutic agents are capable of causing photosensitivity reactions. Phenothiazine derivatives, chlorothiazides, sulfonylurea compounds, demethylchlortetracycline, and griseofulvin are noteworthy examples. Also, the sulfonamides which have long been known to be photosensitizers are still quite useful and widely employed.

Clinical aspects of drug-induced photosensitivity, including comments on differential diagnosis and treatment, were presented and discussed. Considerable emphasis was placed on the fact that photosensitivity may be divided into phototoxic and photoallergic categories.

ACKNOWLEDGMENT

Some of the clinical photographs were available through the courtesy of Dr. E. R. Seale and Dr. J. B. Richardson of Houston.

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THE TRUTH AND THE PATIENT

It is certain that you can, by no possibility, convey to the patient accurate information . . . independently of the associated affective processes. I suggest, therefore, that if you recognize your duty of "telling the truth to the patient," you range yourself outside the class of biologists with liars and philosophers. The notion of the truth, the whole truth, and nothing but the truth can be conveyed to the patient as a good specimen of that class of fallacies called by Whitehead "The Fallacy of Misplaced Concreteness." It results from neglecting factors that cannot be excluded from the concrete situation and that are of an order of magnitude and relevancy that make it imperative to consider them. Of course, another fallacy is also often involved, the belief that diagnosis and prognosis are more certain than they are. But that is another question.—L. J. HENDERSON, 1878-1942.

REMOVAL OF POLLEN AND FUNGI FROM ROOM AIR

Comparison of Window Air Filters and Window Combination Air Conditioners-Air Filters

LEON UNGER, M.D., F.A.C.A., and TYBEE SUE MEYERS, M.T. (A.S.C.P.)
Chicago, Illinois

MECHANICAL DEVICES to filter pollen from the air have been used for many years. Most of them have been more or less helpful in that they are able to remove over 90 per cent of the pollen which enters the filters. Most of these filters have been satisfactory in all respects except one, i.e., they do not supply enough circulating air for the comfort of the patient.

In nine rooms at the Chicago Wesley Memorial Hospital, filters have been used since 1941.** On hot days, the twelve patients in these rooms really suffered because of the relatively small amount of air coming through the window air filters. Those air filters gave even less air when the openings were obstructed by various dusts.

Recently we have tested new air filters and combination air conditioners and air filters.† We have carried out pollen and fungus counts with both types of machines. Slides were exposed in these rooms during the past three ragweed seasons, and the results were compared with slides exposed outdoors on window sills.

TECHNIQUE OF EXPOSURE AND COUNTING

Slides were exposed inside ten hospital rooms and on the outside sill of the corridor window, on the eighth floor of the hospital. Most of the rooms were so-called "asthma" rooms, equipped and furnished for the care of asthmatic patients, i.e., foam rubber or Dacron pillows, rubber mattresses, plastic upholstered chairs, linoleum covered floors. Neither flowers nor smoking were allowed in these rooms.

Slides, labeled and coated with a thin layer of petrolatum mixture, were fastened to the top of the headboards of the beds in the rooms selected. In that way, they were in no danger of being disturbed by either the patient or the hospital personnel, who were informed of the presence of the slide. These slides were changed daily at 9:30 A.M. by the same individual, and the exposed slides placed in covered boxes until they could be examined with a microscope.

Presented at the Seventeenth Annual Congress of The American College of Allergists, March 16, 1961, at the Statler Hilton Hotel, Dallas, Texas.

**We first used Airgard Filters, then Pollen Ex #499.

†(1) Pollen Ex Model #499 (Fig. 1). (2) Pure-Air "99" by Pollen Ex, Model #499-A (Fig. 2). (3) Pollen Ex air conditioners Models #59 & 60 (Fig. 3).
These machines were supplied by: Associated Mills, 307 West Monroe Street, Chicago 6, Illinois.

The slides were stained with Calberla Stain, which is absorbed only by pollen, making identification easier. They were then studied under low power, and when necessary under high power, to confirm the identity of

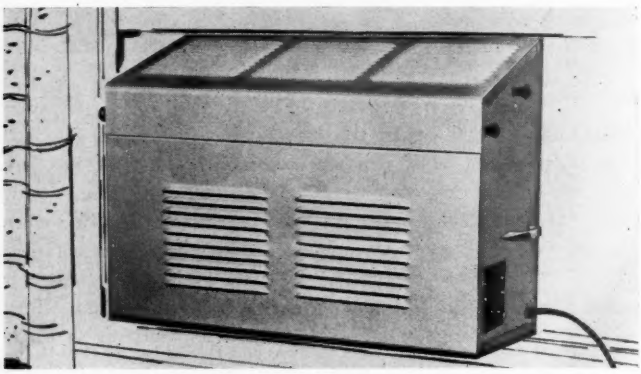


Fig. 1. Air filter, pollen Ex No. 499

Fig. 2. Pure-Air "99" by Pollen Ex No. 499-A.

a pollen grain or fungus spore. All pollen and fungi were counted in an area of 125 square mm under low power, and the results were totaled.

The pollen grains were classified as:

Ragweed Chenopod Miscellaneous Pollen*

*This includes grass pollen.

The fungi spores were classified as:

Alternaria	Rusts	Fusarium
Hormodendrum	Smuts	Stemphyllium
Helminthosporium	Epicoccus	Miscellaneous Fungi*

*Those which cannot be identified without culturing the spore.

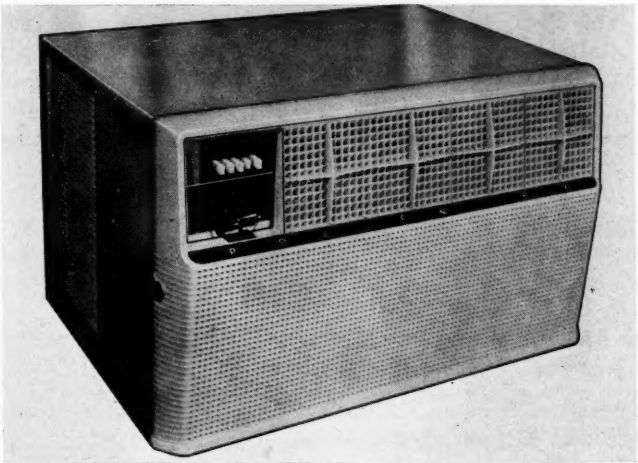


Fig. 3. Pollen Ex, air conditioner-air filter.

TABLE I. POLLEN SLIDES EXPOSED AT WESLEY MEMORIAL HOSPITAL
(August 30th through September 6, 1960)
Total of Eight Days

Location of Slide	Total Pollen	Per Cent of Pollen Removed	Total Fungi	Per Cent of Fungi Removed
Outside	1250		1806	
Air filter No. 499-A, Rm. 891	16	98.72	43	97.63
Air conditioner, air filter, Rm. 887	21	98.32	97	94.65
Air conditioner, air filter, Rm. 892	27	97.84	97	94.27
Air filter No. 499, Rm. 893	27	97.84	68	96.25
Air conditioner, air filter, Rm. 885	32	97.44	175	90.35
Air conditioner, air filter, Rm. 886	33	97.36	82	95.48
Air filter No. 499, Rm. 891	37	97.04	117	93.55

Charts were made of each room's daily counts using the above classification. In order to facilitate the presentation, only total pollen and fungi counts are used in the tabulation of results. The notation "percentage removed" is the comparison of the counts on the slides exposed in the selected rooms to those exposed outside.

MECHANICAL DATA

The filters used in the various models of the Pollen Ex air filter machines are of the same density and thickness, although they vary in dimensions in relation to the size of the machine.

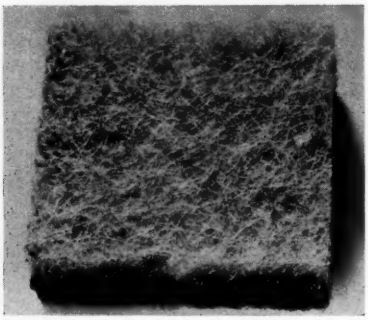


Fig. 4. Pollen Ex filter.

The filter, of impingment fibers, is 2 to 2.5 inches thick and contains three properties (Fig. 4):

1. Permasterile® covers the fibers and has been found to "remove 100 per cent bacteria including Staphylococcus aureus, 209 P."

2. Activated charcoal adheres to every fiber. This is for the removal of smoke, odors and gaseous substances.

3. Chemically treated fibers on the outward side to increase the adhering properties.

The air filter machines use a mixture of outside and inside air. A damper can be regulated to give the percentage of inside air selected. This damper can also be closed completely so that no outside air comes in. During these tests, a maximum of outside air was used. The capacities of the machines are as follows:

#499 Window unit (Fig. 1)	High speed:	245 cubic feet per minute
	Medium speed:	100 cubic feet per minute
	Low speed:	50 cubic feet per minute
#499-A Window unit (Fig. 2)	High speed:	580 cubic feet per minute
	Medium speed:	430 cubic feet per minute
	Low speed:	200 cubic feet per minute

The filters used in the combination filter-cooling machines are thinner but of an increased density. The mixture of air in these combination machines (Fig. 3) is similar to that of the air filter machines. The air flow of the machine is reduced when the filter becomes dirty. Filters should be changed as advised by the manufacturer (about once a month depending on location).

DISCUSSION

The two new machines are both efficient. The air filter number 499-A operates to a maximum of 580 cubic feet per minute, and this machine gives the patient sufficient air and at the same time removes over 98 per cent of pollen and about 97 per cent of fungi.

The combination air conditioner-air filter removes about 97 per cent of pollen and about 94 per cent of fungi—not quite as much as the air filter. In addition, because it is an air conditioner, excess humidity is done away with, and the patients are cool and comfortable. Asthmatic patients, however, are not always benefited by cool air—some patients may do better in simple air-filtered rooms.

We also tested some portable air filters which were placed between the open window and the patient's bed. The amount of pollen and fungi in such rooms was lessened, but these filters were not as efficient as filters placed in the window itself. Such filters remove pollen and fungi only from that part of the air which goes through the filters. Therefore, we recommend efficient filtering machines which can be sealed in the windows.

TABLE II. RESULTS OF SURVEY
(August 30 through September 6, 1960)

Type of Unit	Pollen (Mainly Ragweed) Per Cent Removed	Fungi Per Cent Removed
No. 499, air filter (two rooms)	97.44	94.9
No. 499-A, air filter	98.72	97.63
Air conditioner-air filter (four rooms)	97.74	93.69

SUMMARY

1. Pollen and fungi have been successfully removed by means of a new window-type filter and by a window-type combination air-filter and air-conditioner. Each of these two machines has removed from the air about 97-98 per cent of ragweed pollen, and about 94-97 per cent fungi.

2. This new air filter (499-A) gives sufficient air so that the patient in the room is comfortable.

3. The new combination air-filter and air-conditioner also cools the room and lessens humidity. The cooling may increase asthmatic symptoms in some patients.

4. The machines and technique for counting of pollen and fungi are described.

5. Air filters which are sealed in the window should be efficient because they filter all the air.

6. The filter media of impingment fibers, Permasterile, activated charcoal and chemically treated is 2 to 2.5 inches thick, of very dense construction and is recommended for efficient filtration.

185 North Wabash Avenue, (Dr. Unger)

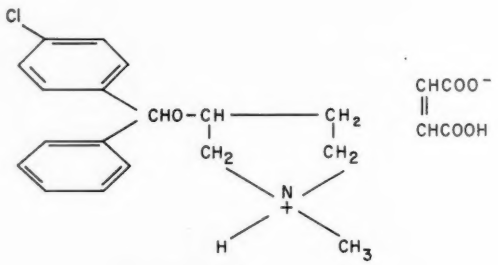
PYROXAMINE: A CLINICAL STUDY OF A NEW ANTIHISTAMINE

J. WARRICK THOMAS, M.D., F.A.C.A.
Richmond, Virginia

BOTH clinicians and pharmaceutical manufacturers are continually alert for new products that will alleviate the distress of patients having varied manifestations of allergy. The antihistaminic agents, of course, have had a wide consideration.[1-3] The recognition of the need for drugs with minimal side effects and drugs that offer a satisfactory clinical response prompted this study.

CHEMISTRY OF THE DRUG

Pyroxamine is a new chemical substance and it may be identified chemically as 3-p-chlorobenzhydroxy-1-methylpyrrolidine maleate. It has the following structure:



PYROXAMINE
3-p-chlorobenzhydroxy-1-methylpyrrolidine maleate

The molecular weight of pyroxamine is 417.87 and it has a melting point of 130-132° C. It is a white powder and only slightly soluble in water.

Pyroxamine may represent a more specific antihistaminic substance by virtue of the more rigid fixation in space of the distances between the oxygen and nitrogen prosthetic groups, serving to produce a more selective binding at the physiological receptor sites, and thereby effectively blocking histamine from access to these sites.

Presented at the Seventeenth Annual Congress of The American College of Allergists, March 15, 1961, Statler Hilton Hotel, Dallas, Texas.

The drug employed in this study was supplied through the courtesy of the Medical Department of the A. H. Robins Company, Inc., Richmond, Virginia.

Dr. Thomas is Assistant Professor of Clinical Medicine, Medical College of Virginia Hospital, and Director of the Thomas Clinic, Richmond, Virginia.

PHARMACOLOGY

Extensive studies in several species of animals have demonstrated that pyroxamine[4] is a highly potent histamine antagonist with a gratifying low toxicity. When compared with other potent and extensively used antihistaminic agents, it was unexcelled by any of them and appeared to be from one and one-half to twenty-five times as effective.

CLINICAL STUDY

In controlled situations, other investigators have shown that pyroxamine is an effective antihistamine of low toxicity in humans. It was therefore decided to evaluate it in a clinical situation, as furnished by private practice.

This study included 172 patients exhibiting primarily either respiratory or dermatological manifestations of allergy that would probably respond to antihistamine therapy. Of these two general divisions there were forty-two patients with skin manifestations of allergy, and 137 with respiratory manifestations.

There was a third category in which patients had frank allergic manifestations in addition to their upper respiratory manifestations of allergy. One patient exhibited allergic conjunctivitis; one, aural allergy (recurrent deafness coincident with rhinitis); and one, gastrointestinal allergy.

RESPONSE TO THERAPY

The response to treatment with pyroxamine was grouped as follows:

Improved: Patients who were pleased with response and were not having any significant distress or side reaction.

Satisfactory: Patients who reported they were symptomatically improved with minimal distress recurrently.

Questionable: Patients who thought at times they were better and at other times experienced some repeated discomfort.

No Change: Patients who experienced no subjective response.

There were forty-five patients with allergic rhinitis (85.2 per cent) who showed a frank improvement or a satisfactory response to treatment out of a total of fifty-four patients. Among forty-two patients with seasonal allergic rhinitis or hay fever, thirty (71.4 per cent) showed a definite response to treatment. There were two patients who showed only a questionable response. In a third category of upper respiratory allergic manifestations there were thirty-one patients who had both the perennial and seasonal allergic rhinitis. Twenty-six (83.9 per cent) of these patients showed a frank response to treatment. Five patients showed no change.

Those patients having dermatological manifestations of allergy included four separate groups as follows: atopic dermatitis—eleven, contact dermatitis—eleven, dermatitis medicamentosa—two, urticaria and angioneurotic edema—eighteen, a grand total of forty-two patients. Twenty-seven (64.5 per cent) of the forty-two cases showed a definite response to treatment,

TABLE I. SUMMARY OF RESULTS OF PYROXAMINE THERAPY IN 172 PATIENTS SHOWING VARIOUS ALLERGIC MANIFESTATIONS

Allergic Manifestations	No. of Patients	Dosage in mg. Per Day						Days of Therapy					Response				
													Improved	Satisfactory	Questionable	No Change	Side Effects
		10	20	30	40	60	80	1	2-7	8-30	31-90	91 270+					
Perennial allergic rhinitis	54	1	10	1	32	10	—	4	5	24	16	4	34	11	0	9	12
Seasonal allergic rhinitis	42	0	6	1	13	24	1	1	14	18	6	3	25	5	2	10	4
Both perennial allergic rhinitis and seasonal allergic rhinitis	31	1	7	2	9	11	—	1	7	17	5	2	22	4	0	5	5
Atopic dermatosis	11	—	—	—	7	3	—	—	3	5	2	1	5	1	2	3	1
Contact dermatosis																	
Drug dermatosis	11	—	1	—	3	6	1	—	2	5	2	2	7	4	—	—	1
Urticaria and angio-neurotic edema	2	—	—	—	2	—	—	—	2	—	—	—	—	1	—	1	1
	18	—	2	1	4	11	—	—	8	8	—	2	7	2	1	8	1
Miscellaneous	3	—	—	—	3	—	—	—	—	1	2	—	2	—	1	—	1
Totals	172	2	26	5	73	65	2	6	41	78	33	14	102	28	6	36	26

and there were three additional patients who had only a questionable response to treatment. Twelve of the forty-two patients experienced no improvement. It was interesting to observe that the disorders of eight of the twelve patients in this group who did not respond were diagnosed as urticaria or angioneurotic edema. This suggests a multiplicity of etiologic components and the difficult control in this type of skin reaction. Out of a group of twenty-two patients having either atopic or contact dermatitis, seventeen of these patients (77.2 per cent) responded to therapy. In addition, two other patients had a questionable response.

DOSAGE PER DAY

Pyroxamine was supplied in a small white scored tablet of 20 mg. The total daily dosage in milligrams by number of patients receiving each dosage is also recorded in Table I. Note that the total daily dosage varied from 10 to 80 milligrams. Seventy-three of the patients were given a total dosage of 40 mg per day or 20 mg of pyroxamine every twelve hours. Sixty-five received a total daily dosage of 60 mg, which reflects a distribution of dosage of 20 mg every eight hours. In reviewing these cases, I concluded that the optimum dosage would range from 40 mg to 60 mg over a twenty-four-hour period. However, there were thirty-one patients who received dosages from 10 mg to 30 mg, the majority of whom received a daily dosage of 20 mg. Some of these patients were children, and the dosage was divided into 10 mg twice daily. Other patients received the dosage of 20 mg on retiring only, and this dosage seemed satisfactory for the majority of this group.

LENGTH OF THERAPY

The patients who received only one day of therapy were those who either experienced side effects from the drug or because of the severity of symptoms refused to take the drug for a longer period. There were forty-one patients who received the drug from two to seven days. This group included a majority of patients having an acute hay fever or seasonal allergic rhinitis or urticaria. They took the drug for this short period because the majority of them obtained either symptomatic relief or no frank response to treatment. Because of their response, the majority of the seventy-eight patients wanted to continue this drug longer than one week. Thirty-three patients were treated for one to three months, and because of the response to treatment, many of them requested that they be continued on this drug. An additional fourteen were on pyroxamine from three to nine months. Three of them continued for a period in excess of six months, and some of them are still on the medication after nine months.

Twenty-two patients exhibited twenty-six side effects as shown in Table II. The majority of the side effects fell under the category of drowsiness.[16] Four of these patients experienced very slight drowsiness. Only eight of the twenty-two patients who discontinued the drug did so because of side effects.

Thus, it might be concluded that in only eight patients (about 5 per cent) out of a total of 172, side effects were sufficient to warrant the discontinuance of the drug.

TABLE II. SIDE EFFECTS OBSERVED IN TWENTY-TWO PATIENTS

Side Reaction	Number
Drowsy	16
Nervous	5
Headache	2
Gastro-intestinal	1
Other	2
Total	26

OTHER ANTIHISTAMINES USED PRIOR TO PYROXAMINE

Of the group of 172 patients on pyroxamine therapy, only fourteen had not previously been treated with one or more antihistaminic agents.

Comparisons of other antihistamines were recorded according to the patient's previous observation as to whether the response was only partial or good. There were forty-six instances in which the patient indicated that

TABLE III. A COMPARISON OF RESPONSE TO PYROXAMINE AND PREVIOUS ANTIHISTAMINE THERAPY

Number of Patients	Antihistamine Therapy
172	Pyroxamine
158	Pyroxamine and previous antihistamine therapy
14	Pyroxamine and no previous antihistamine therapy
56	Reported pyroxamine superior to previous antihistamine therapy
46	Reported other antihistamines superior to pyroxamine
35	Pyroxamine and other antihistamines comparable
21	No opinion of comparison

another antihistamine offered them a better response than pyroxamine, and in fifty-six instances patients reported that pyroxamine was superior to the other antihistamines that were employed. However, it was impossible to correlate definitely the exact antihistamine and dosage which the patient had previously taken. One or more side effects were experienced in forty-five of the 158 patients who had previously received other antihistamines. This observation would reflect the importance in the selection of a specific antihistamine for therapy and a drug that would be least likely to cause side effects. However, there are certain instances in the treatment of patients where the clinician gives an antihistamine for a sedative effect rather than to give the patient some other sedative. It was also observed that in 35

instances patients reported that they received the same response to treatment with other antihistamines as with pyroxamine.

Collateral therapy in the majority of patients consisted of hyposensitization. In patients with an acute dermatitis, topical therapy was also instituted. There were some instances in which questions arose as to whether other forms of therapy might have confused the issue. As a result, these cases were not included in the series.

SUMMARY AND CONCLUSIONS

1. There were 172 patients in this study who presented either upper respiratory manifestations or dermatological manifestations of allergy.
2. One hundred thirty patients (75.6 per cent) responded to treatment; 79.2 per cent of the respiratory group responded; 64.3 per cent of the allergic dermatitis group responded.
3. Pyroxamine therapy and other antihistaminic therapy was compared in 158 patients.
4. Side reactions were minimal, and only 5 per cent were sufficient to stop the use of the drug.
5. This clinical study indicates that pyroxamine is a drug worthy of consideration in the management of dermatological and respiratory manifestations of allergy.

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PSYCHOSOMATICS AND DERMATOLOGY

Physiologic alterations far beyond the normal average may be set into motion by transient, or frequently repeated, severe mental or emotional disturbances, but permanent structural changes do not come into being solely or directly from thoughts, emotions, or mental derangements. The precipitation of some diseases may be made easier or their incidence greater (or of others more difficult or easier on account of mental aberration in directions of deficiency or genius), but macules, papules, pustules, vesicles, wheals, oozing, crusting lichenification, and scars are not caused purely by a disturbed psyche. Neurotic and psychotic individuals may wittingly or unwittingly injure their skins, but without fingernails, knives, or jumps from open windows, nothing they may do in their heads injures the skin especially, or in ways that can be characterized as syndromes.—Morris Leider, Preface, *Practical Pediatric Dermatology,* C. V. Mosby Company, St. Louis, 1956.

Basic Briefs

PATCH TESTING

WILLIAM C. GRATER, M.D., F.A.C.A.

Dallas, Texas

THE PATCH TEST is a specific procedure used to determine the cause of contact dermatitis. Its purpose is to reproduce the skin lesion on an uninvolved area of skin. Like any allergy test, it has its limitations but it has withstood the test of time and has proven of great value in discovering and confirming unsuspected causes. In some cases of industrial dermatitis, it may have medico-legal implications.

HISTORY

Since it has been estimated that there are more than 350,000 organic chemicals, a few thousand inorganic chemicals and several thousand plant species in this country, it is obviously impossible to test for all. Thus the selection of testing materials will rest chiefly on the physician's knowledge of sensitizing agents confirmed by a detailed history. In my own private allergy practice, the articles most frequently encountered are: among plants —poison ivy, ragweed, chrysanthemum, St. Augustine grass; among cosmetics—nail polish, creme-based shampoos, soaps, dyes, and hair lacquers; among metals—chromium, nickel, arsenic and mercury; among dyes—brown and black dyes, especially in dresses; among drugs—streptomycin, Thorazine, Furacin, Benzocaine and mercury compounds; other articles include resins, plastics and shoes. For industrial dermatitis due to contact sensitivity, Table I should be examined.

It should be noted that, in cases of long duration, multiple sensitization is common because patients are more susceptible to sensitization to other allergies. Once sensitivity has been established, its duration is uncertain but is often permanent. What is puzzling is the prolongation of symptoms after contact has been broken. Cross reactions to chemicals of similar structures may occur as, for example, those between oleoresins of pyrethrum, chrysanthemum and ragweed. Mayer[1] has demonstrated a common chemical denominator in related chemicals of the azo dyes and paraphenyldiamine. They break down in the body to the quinone nucleus. These dyes are permitted by the U. S. government in foodstuffs and, in certain patients, may cause a case of dermatitis to remain active.

Presented at the Graduate Instructional Course in Allergy of The American College of Allergists, Dallas, Texas, March 12, 1961.

There is a definite chemical relationship between some sulfonamides and para-aminobenzoic acid, some local anesthetics and some sun filters. This fact explains why a dentist sensitive to novocaine may be sensitive to other anesthetics and often can't use some sulfonamides. It is an explanation also of why a woman sensitive to her hair dye can't wear mink-dyed muskrat, yellow-dyed gloves, nylon stockings or do her own photo developing. It may accordingly be noted that the causes are not proteins, as in atopy, but often lipoids, heavy metals or chemicals.

TABLE I. OCCUPATIONAL CONTACT DERMATITIS

Occupation	*Allergen*
Airplane Workers	plywood, plastic, glues, chromium, woods of cedar and mahogany
Bakers	flour, sugar, cottonseed, cinnamon
Barbers	quinine, resorcin, mercury, capsicum, arsenic, sulfur, creme-based shampoos
Bronzers	arsenic
Burnishers	mercury
Cement Workers	chromium and alkali
Cooks	cleaners, strong soaps, insecticides
Dentists	procaine, metals, sulfas, benzocaine, eugenol
Exterminators	D.D.T., arsenic, formalin, sodium fluoride, lead or pyrethrum
Farmers and Gardeners	plants, arsenic, insecticides, lime dust and fertilizers
Furriers	arsenic, dyes, chromium
Nurses	streptomycin, Thorazine, penicillin, opiates, mercury, formalin, other drugs
Painters	turpentine, varnish remover, arsenic, chromium, linseed oil, aniline dyes
Photographers	pyragallol, metol, chromates, aniline dyes, lacquers
Pottery Workers	cobalt and alkali
Printers	arsenic, chromates, artificial coloring and hydrocarbons in inks
Surgeons	antiseptics used in scrubbing, rubber gloves
Tanners	bichromate and hydrochloric acid

TYPES OF PATCH TESTING

In general, these may be divided into the covered or uncovered patch tests. The uncovered is used for plant oleoresins or a volatile substance which the patient may encounter in industry. A list of oleoresin tests is included (Fig. 1). The covered patch test consists of a small square of gauze to which the test substance is applied. This is then covered by cellophane and then adhesive or scotch tape. The impermeable material seals in the testing substances and is probably slightly irritative. It is believed by many investigators that a good sensitizing agent must also be a primary irritant in high concentration. Commercial patch test plasters are available and are often most convenient. If the investigator uses raw materials from a patient's environment, he must trial-test volunteers to make certain he is not using a primary irritant.

PREPARATION OF PATCH TEST MATERIALS

Several tables have been published in various dermatology texts[2,3,4,7] which give both diluting material and strength of testing preparations.

OLEORESIN TESTS

SET No. 1	SET No. 2	SET No. 3
Yarrow	Quackgrass	American Elm
Western Water Hemp	Redtop Grass	Ash
Redroot Pigweed	Little Bluestem	Black Walnut
Short Ragweed	Prairie Threeawn	Box Elder
Dog Fennel	Sideoats Grama	Catalpa
Common Wormwood	Downy Brome Grass	China-Berry
Manyflowered Aster	Buffalo Grass	Cottonwood
American Thistle	Grass Bur	Hackberry
Lamb's Quarters	Windmill Grass	Hickory
False Ragweed	Bermuda Grass	Honey Locust
Sneezeweed	Alkali Grass	Mesquite
Sunflower	Barnyard Grass	Mimosa
Burweed Marsh Elder	Yard Grass	Mulberry
Wild Lettuce	Wild Rye Grass	Oak
Mare's Tail	Stink Grass	Osage Orange
White Sweet Clover	Wild Barley	Persimmon
Wild Feverfew	Sprangletop	Pine
Blackeyed Susan	Witch Grass	Plum
Russian Thistle	Dallis Grass	Poplar
Horse Nettle	Kentucky Bluegrass	Redbud
Goldenrod	Green Foxtail Grass	Red Cedar
Dandelion	Johnson Grass	Spruce
Poison Ivy	St. Augustine Grass	Sycamore
Ironweed	Needle Grass	Tree of Heaven
Cocklebur	Crabgrass	Willow

SET No. 4	SET No. 5	SET No. 6
Bergamot	Amur Privet	Alfalfa
Blue Myrtle	Arbor Vitae	Asparagus
Calendula	Bird of Paradise	Broccoli
Chrysanthemum	Clematis	Carrot
Coreopsis	Devil's Ivy	Celery
Corn Flower	English Ivy	Corn
Cosmos	Forsythia	Flax
Dahlia	Grapevine	Grapefruit
Feverfew	Honey-Suckle	Green Bean
Four o'Clock	Lantana	Irish Potato
Gaillardia	Lavender	Lettuce
Geranium	Lilac	Mustard
Hollyhock	Mock Orange	Oats
Iris	Morning Glory	Okra
Jonquil	Oleander	Orange
Larkspur	Pyrocantha	Parsnip
Marigold	Queen's Wreath	Radish
Petunia	Salt Cedar	Salsify
Primrose	Scarlet Sage	Sorghum
Shasta Daisy	Snowball	Soybean
Snapdragon	Spirea	Spinach
Stock	Trumpet Vine	Squash
Tansy	Virginia Creeper	Tomato
Verbena	Wisteria	Turnip
Zinnia	Yellow Jasmine	Wheat

Fig. 1.

These tests apply to most skins, however, and any patient may have a different reactive threshold A dilute chemical which may be non-irritating to one person may be quite irritating to another. Table II lists fifty common chemical tests and their strength and diluting substance. Quantitative patch testing is the most precise means of determining the degree of sensitivity.

TABLE II. PATCH TESTS

	Test		*Diluent*
1.	Alizarin	1%	Propylene Glycol
2.	Aniline Blue	10%	Propylene Glycol
3.	Argyrol	10%	Aqueous
4.	Benzocaine	5%	Petrolatum
5.	Bismark Brown	5%	Propylene Glycol
6.	Butesin Picrate	1%	Petrolatum
7.	Camphor Oil	As is	
8.	Chloral Hydrate	10%	Aqueous
9.	Coal Tar	5%	Petrolatum
10.	Copper Sulfate	1%	Aqueous
11.	D.D.T.	25%	Alcohol
12.	Flit	25%	Olive Oil
13.	Formaldehyde	.5%	Aqueous
14.	Furacin	As is	
15.	Gulf Spray	25%	Olive Oil
16.	Lanolin	As is	
17.	Lavender Oil	As is	
18.	Lead Acetate	1%	Aqueous
19.	Linseed Oil	As is	
20.	Lycopodium	20%	Petrolatum
21.	Mercury Bichloride	.1%	Aqueous
22.	Methyl Orange	5%	Petrolatum
23.	Monilia	10%	Saline
24.	Nail Polish	As is	
25.	Nickel Sulfate	5%	Aqueous
26.	Nicotine Sulfate	10%	Olive Oil
27.	Novocain	1%	Petrolatum
28.	Nupercain	2%	Petrolatum
29.	Nylon	As is	
30.	Oil of Bergamot	10%	Petrolatum
31.	Oil of Citronella	10%	Petrolatum
32.	Oil Red	2%	Petrolatum
33.	Orange Oil	1%	Acetone
34.	Orris Root	20%	Petrolatum
35.	Paraphenylenediamine	2%	Propylene Glycol
36.	Potassium Dichromate	.5%	Aqueous
37.	Potassium Iodide	25%	Aqueous
38.	Penicillin	10%	Petrolatum
39.	Pyrethrum	20%	Petrolatum
40.	Resorcinal	3%	Petrolatum
41.	Sodium Arsenate	10%	Petrolatum
42.	Streptomycin	10%	Petrolatum
43.	Sudan III	5%	Petrolatum
44.	Sulfur	5%	Petrolatum
45.	Surfacain	1%	Petrolatum
46.	Solution of Metaphen	1:200	Aqueous
47.	Tragacanth	25%	Aqueous
48.	Turpentine	30%	Petrolatum
49.	Trichophyton	10%	Saline
50.	Zinc Oxide	20%	Petrolatum

PRECAUTIONS TO BE FOLLOWED

1. Avoid primary irritants unless they are adequately diluted.
2. Avoid patch tests in an acute or widespread dermatitis.
3. Avoid testing repeatedly with agents known to sensitize skin easily.
4. Avoid keeping test material on skin too long (never more than five days).

GRADATION OF TESTS

1. 1 plus: Erythema at site of contact.

2. 2 plus: Erythema and edema at site of contact.
3. 3 plus: Erythema, edema and beginning vesiculation.
4. 4 plus: Erythema, edema, distinct vesiculation and, at times, ulceration.

It should be kept in mind that the primary pathological lesion of acute contact dermatitis is an intra-epidermal vesicle. This is associated with dilatation of the blood vessels in the papillary layers, followed by exudation of lymphocytes and plasma. The cells are mononuclear. In case of superimposed infection, the cells are polymorphonuclear. Since the process is a slow one, patches are generally read at forty-eight hours. If a patient is uncomfortable with any patch, however, it may be removed earlier. Sometimes dress dermatitis patches may be kept on for seventy two hours. Generally, the exposed portions of the skin, especially those involved, are the most sensitive. For convenience in multiple testing, it is often sufficient to use the back. Only rarely is it necessary to test the involved area. Systemic corticosteroid hormones, but not antihistamines, will reduce the reaction.

INTERPRETATION OF PATCH TESTS

Interpretation involves the clinical judgment of the investigator. Generally, if a clear history of contact is followed in hours or days by trouble, combined with a strong positive patch, the diagnosis is obvious. A negative test may indicate a lack of sensitivity but also a failure to reproduce the conditions responsible such as heat, irritation, friction or sunlight. Multiple sensitizations in chronic cases are common, and it may be difficult to determine the exact cause. False positives may be obtained from primary chemical irritation, infection or the red color of dyes in lipstick and nail polish. With these admitted problems, patch testing, properly applied, still remains a most effective, satisfactory procedure for the diagnosis of contact dermatitis. It is one of the few tests in clinical medicine that attempts to reproduce the lesion in miniature by actual contact with the cause.

SOURCE MATERIALS

1. Chemical Patches: Hugh Graham Laboratories, Inc., P.O. Box 14197, Dallas 34, Texas
2. Hypoallergic Cosmetic Testing Kits: Texas Pharmaceuticals (Almay; Marcelle), Dallas, Texas
3. Patches—Elastopatch: Duke Laboratories, South Norwark, Connecticut
4. Plant Oleoresins: Hugh Graham Laboratories, Inc., P.O. Box 14197, Dallas 34, Texas

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Historical Document

1922

BRONCHIAL ASTHMA AND ALLIED CONDITIONS

Clinical and Immunological Observations

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IN ASTHMA clinic was established in the out-patient department of Bellevue Hospital, New York City, in October, 1919. For the year 1919-1920, the scope of the work included a detailed study of the clinical aspects of asthma, which was published.[1] During the year 1920-1921 the following investigations were attempted, the results of which are embraced in this paper: (a) A continued study of the clinical considerations of asthma, (b) observations on skin reactions, (c) effects of vaccine therapy.

During the year, 105 cases of bronchial asthma were studied in detail, twenty-five of pollen sensitization, two of urticaria, and two of angioneurotic edema.

CLINICAL OBSERVATIONS

From a practical standpoint, it is important that cases of bronchial asthma be recognized clinically as speedily as possible, since special methods for diagnosis and relief of the condition are attempted. The urgency of the presenting symptom, however, leads to quick transfer to the asthma clinic, when the dyspnea is supposedly asthmatic. The first task of the clinic, therefore, is to eliminate those cases which do not belong to it.

Apparently, the most frequent diseases superficially mistaken for bronchial asthma in this clinic are: Chronic cardiac disease, chronic nephritis, acute bronchitis, chronic pulmonary tuberculosis; much less frequently subjective dyspnea in "nervous" subjects, hysterical tachypnea, obesity, and early lobar pneumonia in advanced age. All of these patients have complained of "wheezing" and "choking," and some presented chest signs not unlike bronchial asthma. Through lack of careful history and physical examination, these patients were referred to the asthma clinic.

After such elimination, there is left a large group of cases complaining of difficult respiration (usually described as "wheezing," "choking," or "tight breathing"), which comes on periodically, and especially at night. In some cases, particular stress is laid on cough and expectoration, which may be entirely absent in other cases. It is well known that the characteristic

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EDITOR'S NOTE: Tables have been omitted to save space.

Reprinted from the *Journal of Immunology*, 7:81, 1922.

physical signs of bronchial asthma, chronic bronchitis, pulmonary emphysema, may or may not be elicited.

It is in these patients that special means of differentiation are followed. We have attempted to divide them under the following headings:

1. Bronchial asthma; simple, uncomplicated.
2. Chronic bronchial infection with its complications, simulating bronchial asthma.
3. Bronchial asthma, complicated by chronic bronchitis.

Possibly a fourth type, as yet unrecognized, may be chronic bronchitis complicated by bronchial asthma, and not merely simulating it—including those who have acquired sensitization to bacterial proteins.

The first type is well defined. It is characterized by a frequent family history of bronchial asthma, hay fever, or other allergic conditions; early age of onset; past history of hay fever, urticaria, eczema, or angioneurotic edema. The paroxysms are sudden in onset, and are usually *followed* by cough, with production of mucoid sputum. Physical examination often reveals the constitutional defect of status lymphaticus or its borderline conditions. Likewise, the blood pressure is characteristically low, and there is often increased sensitiveness to epinephrin. There is absence of evidences of bronchitis, and relative infrequency of emphysema, as shown by physical examination and x-ray. This group shows a high percentage of skin reactions to foreign proteins.

Eosinophilia in the blood is present in this type of simple bronchial asthma. The sputum, on gross examination, as seen in Petri plates against a black background, is homogeneous, viscid, and transparent, excepting the small hazy coiled streaks known as "perles." Large masses of eosinophiles are present, as many as 50 per oil immersion field. Polymorphonuclear neutrophiles are relatively few.

The characteristics of the second type (bronchial infection simulating bronchial asthma) are in contrast with that of the first. A late age of onset is the rule, with history of cough, and profuse expectoration of long standing, preceding the asthmatic symptom. They do not give histories of allergic conditions, as mentioned in the above group, or family histories of these ailments. They usually state that their attacks "begin with a cold." Cough and expectoration are always prominent, and *precede* the attacks, which are not sudden, without warning, as in the first type.

Physical examination usually shows the signs produced by exudate in the bronchioles and bronchi, whether the patient is suffering from asthmatic dyspnea or not. Pulmonary emphysema is frequent. In contrast to the first type, in which constitutional defects were found to be common, the physique is usually robust. Blood pressures are not characteristically low, and the response to epinephrin is normal. They do not, as a class, show sensitiveness to foreign protein.

The third type is primarily type 1, on which infection is superimposed. It is differentiated from the second type by the history, physical examina-

tion, and sputum, all of which retain characteristics of the first type. The sputum is mucoid, containing varying amounts of mucopurulent material. "Perles," when seen, are opaque. Polymorphonuclear neutrophile cells are prominent in proportion as the infection dominates the original condition.

IMMUNOLOGICAL REACTIONS

During the year, observations were made on the "skin reaction" as a diagnostic aid in asthma and allied conditions. The mechanism of the reaction has not been established. That the skin reaction sometimes demonstrates the exciting cause of symptoms, is a well known fact. Since often no amount of questioning reveals the cause, and as the removal of it gives immediate relief, there is justification for continued study of this diagnostic aid.

A certain proportion of individuals suffering with asthma or hay fever react with the formation of an urticarial wheal when a small amount of the substance which can originate an attack is brought in contact with a scratch, or injected into the skin. The wheal exhibits irregular edges and pseudopodia develop within twenty minutes, and are usually surrounded by an area of erythema, accompanied sometimes by swelling and other signs of inflammation. The site itches and occasionally remains red and swollen for several days. Regardless of method employed, a marked reaction in a definitely sensitive skin never is difficult to elicit.

COMPARISON OF METHODS

More tests can be made with less trouble, and time, at the same sitting, with the scratch method. The resulting mark, which, in unusual cases, may last several months, is more pronounced with the scratch than with the intracutaneous method. With dry preparations there is no way in which to tell when they have lost their potency. With solutions, contaminations which destroy the potency can be readily seen. Also, when a precipitate forms in a solution, the potency may be decreasing. One such solution which had given very good reactions for several months, developed a precipitate. Cultures proved it to be sterile. Upon testing, negative reactions were obtained in some skins which then reacted well to a fresh solution.

For an out patient dispensary where expense had to be considered, an inexpensive syringe was devised, and has given satisfactory service during the past six months. This consists of a simple capillary tube of "non-sol" glass, with a flange at the wide end, over which a rubber bulb, with a thick wall, and one large perforation, is fitted.

Clinical results showed that the slight tenchical *(sic)* advantages of the scratch method were outweighed by the increased reliability of the intracutaneous method.

To illustrate with a case:

A. B. developed asthma only when in contact with horses. A horse could pass, or he could ride a horse for a few minutes without symptoms, but after close contact

for four or five minutes, he invariably began to wheeze. On May 1, 1929, he was tested intracutaneously on the right forearm with a solution of horse dander prepared by Dr. Coca's method. Two inches away, on the same arm, a dry commercial preparation was applied by means of a ⅛-inch superficial scratch, upon which a drop of $\frac{N}{10}$—NaOH was applied, and then dry powder stirred into it. A control injection of horse serum was made. After twenty minutes, the intracutaneous reactions showed an irregular wheal, 3 by 2.5 cm., surrounded by erythema. The patient complained of itching at the site of injection. There was no reaction at the site of the scratch. The solution of horse dander, which gave this reaction, was injected into ten other asthma patients with negative results. The horse serum gave no reaction. Similarly it was found that in fifteen instances . . . there was no definite response to the commercial preparations put on by the scratch method, although history and intracutaneous tests were positive. The ragweed and timothy scratch reactions performed with commercial solutions proved to be potent on the more sentitive *(sic)* skins. The dog hair, cat hair, chicken feather, and rabbit hair dry preparations had been received within three months and were then kept dry in the laboratory. The commercial pollen extracts gave a good reaction in most cases. The dry products, however, although effective in most cases, were so uncertain that they were unsatisfactory for routine use. . . .

It is not possible to use the calibration devised by Walker in comparing these two methods. One can make no definite ruling as to the reading of reactions. Some reactions up to 1 cm in diameter were considered negative. The normal varies with different skins. The normal on an irritable skin cannot be compared with the normal on an unresponsive skin. It emphasizes the fact that questionably positive reactions must be measured parallel with control reactions on the same individual. These are the borderline reactions; they occur with the scratch as well as with the intracutaneous method. In such cases, an opinion can be arrived at only by repeated tests on different days, and with careful investigation of possible contact. Another well-known fact which has at times led to misinterpretation, is a positive reaction in a clinically non-sensitive individual. One such positive reaction will not necessarily establish a diagnosis.

COMPARISON OF THE TWO METHODS WITH THE SAME SOLUTIONS

To compare the scratch and intracutaneous methods on the same individual with the same solutions, the following experiment was performed: Ten patients known to be sensitive to ragweed pollen were injected on the anterior surface of the forearm, using four solutions of different strengths of ragweed pollen. Solution A, ragweed solution with 0.3 per thousand nitrogen content. The other three were freshly made solutions. (Coca method). Solution B, 1:100; Solution C, 1:1000; Solution D, 1:5000. Weight of pollen in grams was the factor used in determining the strength of dilutions. The middle anterior one-third of the forearm was used, alternately placing the strongest solution superiorly and inferiorly on the different patients. Two inches away, and parallel with the injections, scratches were made about ⅛ inch long, and deep enough so that small

red points were just visible. These scratches were kept covered with the various solutions for twenty minutes. At the end of that time, readings were made by measuring the longest and broadest diameter in millimeters. The results are tabulated in Table II. The two strongest solutions were injected at the same time into two normal individuals, and had been used on many other patients without reactions. Control solutions were also used on all these sensitive cases with negative results.

It is therefore evident that certain individuals, whose asthma or hay fever is brought on by specific proteins, may give a skin reaction to a solution of that protein when it is injected intracutaneously, and show no reaction when the same solution is applied by means of a scratch. Walker[2] also found this to hold true.

RELATION OF SIZE OF SCRATCH TO SIZE OF REACTION

To determine whether the size of the scratch influences the size of the reaction, the following experiment was performed: As in the above experiment, the middle anterior third of the forearm was used. Eleven patients whose skins were definitely sensitive to ragweed were chosen. Two or more scratches of lengths varying from 1 to 11.5 mm, and just deep enough to draw blood, were made. The scratches were covered with decinormal NaOH and dry ragweed pollen mixed with the fluid. The reactions were read in twenty minutes. . . . The size of reaction in breadth varies with the length of the cut, but not directly, due perhaps to the irregular distribution of lymph spaces and channels.

INFLUENCE OF LOCATION ON REACTION

Schloss[3] believes that the size of reaction varies, depending upon the location on the arm. To test this statement, fourteen sensitive patients were given intracutaneous injections of ragweed pollen solution at the elbow fold anteriorly, and a second injection of this solution, of like amount, was given 10 cm below. The reactions were read in twenty minutes. . . . The reaction at the elbow was never smaller, and was usually larger than the reaction at the region nearer the wrist. There was always more erythema at the elbow site.

Another factor which influences the size of reaction is the degree of sensitivity of the cells. This does not appear to be proportionate to the severity of the clinical symptoms. The reactive power of the skin is variable, since the same solution of ragweed, injected in like amounts into the skins of one normal and two sensitive individuals gave the following experimental results. The first showed no reaction while the two sensitive patients showed wheals. One of the wheals measured 2 cm in diameter, the other 10 cm by 5 cm.

Again, the strength of the protein solution brought in contact with the cells is a factor which helps to determine the size of reaction. This is shown in Table II, where the same amount of fluid was injected in each

instance. Some individuals fail to respond to a dilution in which the protein proportion is less than 1:100. This fact has been made use of to determine the initial dose of curative injection.

When different quantities of protein solutions of equal strength are employed, a similar relation is noted. Eight sensitive patients were injected on the right forearm with 0.01 cc and 0.04 cc of a ragweed solution containing 0.3 mgm of nitrogen per cubic centimeter. The reactions were measured at the end of twenty minutes. The results are shown in Figure 3. The size of wheal is shown to increase with increase in the amount of protein solution injection, though not always in proportion with it.

VARIATIONS IN SKIN REACTIONS AT DIFFERENT TIMES

Another point noted was a variation in the skin reaction from week to week. In fourteen sensitive cases receiving identical inoculations of ragweed pollen solutions, reactions were measured for a period of several weeks. In no case did the skin reaction become negative. In eleven cases there was a definite decrease, both as to size of wheal, amount of erythema, itching, and duration of resultant swelling. The effect was more marked in cases which had at first given violent reactions. In the remaining three cases, there seemed to be no change in the response. That, after a series of prophylactic inoculations, an individual can go through a season without symptoms, and yet constantly show a positive skin reaction, is well known. Normal variations were also watched in sensitive cases not under treatment. The question whether the skin reaction shows variation in intensity, or complete disappearance at different times, is being studied.

The skin reactions were, therefore, found to be influenced by the following factors: (a) The preparation used; (b) the method of application; (c) the length of scratch made; (d) the site of injection; (e) the degree of cellular sensitivity; (f) the amount of protein brought in contact with the cells, and the amount of solution injected.

LOCAL SKIN DESENSITIZATION

A point still in question is local skin desensitization. Mackenzie[4] showed that by repeated injections at the same site on the same day, he could cause a disappearance of the reaction. This was repeated on two cases, as follows: The first was a male nurse sensitive to timothy pollen. He was injected nine times in the same site with timothy solution, 0.6 mgm of nitrogen per centimeter. The first injection was given at 9:30 a.m.; the last at 6:30 p.m. The injections were approximately one hour apart. Due to the erythema and swelling which remained, it was difficult to gauge the amount injected each time. After no injection, however, did the skin fail to respond with a new wheal. After the eighth injection, the patient had symptoms of hay fever; also two hours after the ninth. The eighth and ninth reactions were the largest, giving wheals with irregular edges and pseudopodia. The next morning, the forearm was still red and swollen,

and another injection at the same site was followed by a markedly positive reaction.

The second case was a ragweed sensitive patient. Four injections were given during the course of an afternoon. After no injection did the cells fail to respond, and there was apparently no decrease in reaction.

To test out the effect of weekly injections at the same site, two patients were used. After several injections, there seemed to be a definite decrease in the reactive power of these cells. The wheal became smaller, the erythema less, and when seen on the succeeding day, the site of continuous injection was clear. The control (new site) still showed a swollen area of erythema several centimeters in diameter. One patient was sensitive to both ragweed and timothy. Both decreased as stated above, and after three months the injections were reversed, the cells responded as at a new site. Injections were then discontinued for a period of three weeks. When the site was then inoculated, it responded as a fresh site. On the following day, it was still red and swollen as badly as the control site. The effect was apparently only temporary, and there was no permanent increase or decrease in the power of the local cells to react.

GENERAL REACTIONS FOLLOWING INTRACUTANEOUS INJECTIONS

One of our patients developed symptoms of hay fever after a test injection. Another patient, a nurse who had infrequent attacks of asthma, was tested out with a great variety of proteins without result. She had noticed that, after being in the ward where the children had their hair treated with delphinium, she always felt tightness in her chest. She was injected with a very small amount of the tincture of delphinium into the skin. In ten minutes no wheal appeared. Twenty minutes later, there was a large wheal at the site of injection, and an attack of asthma occurred, worse than any heretofore. Ten minims of adrenalin relieved her. Two hours later, she suddenly broke out with intense urticaria, the wheals developing over her entire body, head and extremities, with intense itching. Again in two hours she had another attack of asthma, which was again relieved by adrenalin. She has been feeling perfectly well since, but she has been careful to avoid contact with delphinium.

Several of the patients, after the first injection, had swollen and red arms. In one instance, the swelling and redness extended to six inches above the elbow. There was no pain, and the patient continued with his work. These untoward reactions are unusual.

VACCINE THERAPY

Recognizing the association of evidences of bronchial infection and asthma in many cases, the effects of vaccine therapy were studied. At the outset, autogenous vaccines were made from the predominating organisms in washed bronchial sputum specimens. Most of these bacteria were Gram-positive cocci. Eleven patients were so treated. The initial dose was

approximately one hundred million, and the interval once a week. Ninety-four injections in all were given. Clinical improvement in such cases must be measured largely by the patients' statements. Eight cases were thus recorded distinctly improved; there was no change in the remaining three.

After several weeks of such treatment, many of the vaccines were lost through an accident. Temporarily, two vaccines were used, each of a virulent staphylococcus aureus strain, and it was surprising to find that apparent clinical improvement continued regardless of the nature of the organism predominant in the patient's sputum.

An effort was then made to determine whether this effect were merely one of non-specific protein, and a typhoid-paratyphoid stock vaccine mixture was next given. Although slight continued improvement was noted in six of the thirteen cases treated, two who had been doing well on the former regime, became distinctly worse. No improvement was noted in the remaining four.

After six weeks of this treatment, a stock staphylococcus vaccine was used, and seventeen cases were treated with this. Improvement was recorded in ten, questionable improvement in one, and none in the remaining six.

The best results were obtained when vaccines were given in relatively small doses (100,000,000 of staphylococcus aureus), at the outset, with an increment never larger than the original dose. Two interesting observations were made: This dose would frequently cause improvement for but three or four days, and was more effective when given twice a week. Likewise, when the dosage was increased too rapidly, relapse would frequently occur. In some cases where improvement was not recorded, the asthmatic paroxysms disappeared, but the cough became worse.

The difference in effect of the various types of vaccine is not impressive, excepting that in no instance when typhoid vaccine was used, did the degree of improvement approximate that of the other organisms employed. Too few cases have been treated, to draw conclusions, but the inference is made, that, in asthma associated with signs of bronchial infection, vaccines, if given cautiously, are worth a trial. In some instances where other measures availed little, improvement began almost immediately after vaccine therapy was instituted. In others, the results were wholly disappointing. How these agents act, has not been determined, and further study is planned.

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Progress in Allergy

HUMAN ECOLOGY AND SUSCEPTIBILITY TO THE CHEMICAL ENVIRONMENT

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(Continued from June issue)

Part IV. Chemical Contamination of Ingestants

A. FOOD ADDITIVES AND CONTAMINANTS

SUSCEPTIBILITY to chemical additives and contaminants of the diet has long been confused with specific susceptibility to foods as such.[8] This confusion should have been expected, since both apparently involve adaptation processes; both commonly co-exist in the same individual; manifest in similar symptoms and are exceedingly difficult to separate. In fact, separation did not occur until reliable sources of relatively non-contaminated food became available for test purposes. Only then did it become evident that at least certain patients, originally thought to have been sensitive to certain *foods,* turned out to have a major *chemical food contamination* problem. Others were found to be primarily food sensitive but with slight, if any, demonstrable susceptibility to chemical additives and contaminants of the diet.

The separation of these two closely related conditions also provided answers to several previously baffling observations—data that at times had been used to discredit the existence of specific food susceptibility. Most troublesome to explain was the inconsistency of a given food to induce clinical reactions in patients known to have been highly susceptible to that food when the same item from different sources was fed under otherwise identical conditions of testing. Rowe's observations of the frequency of multiple fruit sensitization—at variance with the tendency for involvement of the diet to follow botanical groupings[23]—and the apparent accentuation of food allergy during winter months[32] also remained unexplained.

It should be emphasized that the observations to be reported—differentiating *reactions from chemical additives and contaminants of foods* from *susceptibility to foods per se*—should be made with a full understanding of the dynamic nature of both processes. Although the nature of the chemical problem is described herewith, the reader is referred to other sources for descriptions of food susceptibility or food allergy.[8,13,16] Test

procedures, in both instances, should be carried out during non-adapted phases of reaction, as described earlier in this article.

Observations of a physician-patient, known to have been highly susceptible to apples and peaches, initiated this interest. Although he developed a headache each time he ate commercially available peaches or apples, he found that he was able to eat these home-grown *unsprayed* fruits with impunity. These observations remained unexplained until interpreted on the basis of the cultural and technological contamination of these foods, on the one hand, and this patient's susceptibility to numerous chemical exposures, on the other. As these leads were pursued and chemically uncontaminated foods became available for test purposes, these inconsistencies in the results of repeated individual food ingestion tests were explained. Moreover, certain of these patients appeared to react more definitely to these commercially available and relatively contaminated foods during *winter months* when concomitantly exposed to heavy concentrations of indoor chemical air pollution.

Some of these patients also remained chronically ill in Chicago at any time of the year. Their illness was apparently the result of exposure to *outdoor chemical air pollution* because they improved in rural areas, if the major sources of chemical contaminants of their living quarters, diet and water supplies had been controlled. In others, the additional effects of pollens, spores, dusts and seasonal chemical exposures superimposed other reaction patterns.

These points illustrate the multiplicity of interrelationship of impinging exposures as far as an afflicted individual is concerned. Presentation of the subject unfortunately necessitates first an arbitrary division limited to food contaminants and subdivisions of that subject.

Spray Residues

So-called Multiple Fruit Sensitization.—Three patients, clinically susceptible to multiple chemical exposures, were selected for a preliminary study. After eating peaches they manifested severe urticaria, asthma and headache, respectively. Commercial peaches purchased on the market and similar ones from an abandoned orchard were employed as unknowns. All three reacted to the ingestion of the commercial fruit but failed to react to the technologically uncontaminated peaches.[33]

The following season, four lots of peaches were tested in like manner in fifteen additional subjects. Although the same type of peach was used in all tests, their technology differed as follows: (1) Peaches picked from trees of an abandoned orchard, having received no sprays, fungicidal treatment or fertilization for the previous three years. (2) Same as the above except that the fruit had been manually dusted with sulfur as a fungicidal measure. (3) Peaches from one of the University of Illinois Department of Horticulture plots which had received the recommended

spray schedules using DDT and Dieldrin. (4) Peaches from the same source sprayed with Parathione and Dieldrin.*

For several days prior to each blind ingestion test, all subjects had been avoiding both peaches and chemical exposures to which they had been known to be susceptible. Three of the fifteen subjects were made acutely ill following the ingestion of chemically *uncontaminated* peaches. In contrast to this small group, a larger number of the others reacted to both the *sulfured* and the *sprayed* peaches. The severity of these reactions in some instances dissuaded them from continuing with the battery of blind ingestion tests. Because of this, the series was never completed. But because several who were negative to the controls reacted to each type of contamination, it may be said that there was something about both the sulfured peaches and those treated with insecticide-solvent mixtures that precipitated *acute* reactions. There were no apparent differences in the degree or severity of reactions between the two types of sprayed peaches; each person who had been tested to both sprayed lots reacted to both. Whether the active ingredient of the spray or the oil vehicle was responsible for the reactions was not determined.

From subsequent observations in many other similar patients, the presence of clinical reactions to several commercially available fruits—irrespective of their botanical groupings—suggests the presence of susceptibility to a common technology associated with *fruit culture* rather than a *multiple specific food allergy.* The greater the background of susceptibility to chemical contaminants in a given case, the more likely this interpretation, although multiple fruit sensitization, in the absence of demonstrable susceptibility to the chemical environment, may occur. It is of special interest that the majority who had been avoiding numerous fruits for many years have since been able to eat most of the previously suspected chemically less-contaminated fruits.

In general, the scope of this so-called "multiple fruit sensitivity" is variable from patient to patient, being the more inclusive in those with the greatest degree of susceptibility to *chemical* exposures. Peaches, apples and cherries seem to be the most commonly contaminated as well as heaviest in their contamination. Although the total number of spraying applications varies with rainfall and other conditions, peaches, apples and cherries may be sprayed between ten and fifteen times per season. Recommended spray schedules start with blossoming and end only a few weeks prior to harvesting. The fact remains, however, that most commercially produced fruits in the United States are *copiously sprayed,* some are dusted with sulfur, some fumigated or otherwise contaminated in growth or handling, as will be described. Since the technology of a given fruit may involve several possible chemical contaminations, it often requires considerable experimentation to be certain that a *given additive* is the *cause* of a *given reaction.*

*Furnished through the courtesy of Dr. George Decker, Department of Entomology.

Once a fruit has been sprayed with a combination of chlorinated hydrocarbons and kerosene or some other chemically derived insecticide-solvent mixture, *there is no known way of removing such spray residues.* Since a growing or stored fruit has a continuous exchange of air between it and its surroundings, these spray ingredients apparently become *incorporated into the pulp of the fruit.* Washing, rubbing, peeling, cooking or combinations of these processes do not eliminate spray residues, as judged by the ability of fruits so contaminated to precipitate acute reactions when ingested as unknowns by highly susceptible persons. Nevertheless, there is a group of lesser susceptible persons who, when *avoiding* other chemical exposures, may be able to eat commercially available *stewed* fruits although unable to eat the same lot of *fresh* fruit. Since these spray residues are at least partially volatile, this may account for the common observation that stewed fruits seem to be better tolerated by some individuals than the same fruits in their raw state. In keeping with this view is the fact that *inhalation of the odors of chemically contaminated* stewing fruits and vegetables have precipitated clinical reactions in some, although cooking odors of the same items *not so contaminated* have been tolerated.

However, even highly susceptible persons eating a general diet rarely suspect the daily ingestion of fruits containing the usual spray residues. These conditions simply tend to perpetuate chronic symptoms. Only occasionally, when the intake of chemical contaminants may be excessively high, does such a dose break through this level of chronic symptoms so as to induce an acute obvious reaction.

So-called Multiple Vegetable Sensitivity.—Individuals susceptible to various other chemical exposures often are unable to eat cabbage, broccoli, cauliflower, celery, lettuce, spinach, beet greens and certain other leafy vegetables belonging to various botanical families. Several such patients have been found susceptible to *sprayed* vegetables but not to the same vegetables *unsprayed.* Of this group, the members of the cabbage family seem to be the most copiously contaminated. Whereas all cooks were formerly alerted to the presence of cabbage worms on broccoli, the writer has not known of anyone who uses commercially available vegetables encountering worms on broccoli during the past decade.

Other practices contributing to the spray contamination of foods is the *indiscriminate spraying of fruit and vegetable counters* in retail markets. This apparently is done to control fruit flies. Susceptible persons usually start to cough, wheeze, or manifest some other evidence of reaction when in this area of markets. Admittedly, these reactions are difficult to differentiate from those attributable to the evaporation of previously applied spray-solvent mixtures as well as those from the inhalation of deodorants, disinfectants and cleaners used in the markets. The fact that the majority of such reactions occur in the vicinity of the produce counters and the

fact that spraying of such areas is known to be a common practice suggests this exposure as the predominant one.

Spray Residues and Other Contaminants of Meat and Poultry

The fat of certain commercially available meat, especially lamb, beef and some poultry, is apparently contaminated chemically. This is judged by the ability of such fats to induce symptoms in patients highly susceptible to certain other chemical exposures. The major sources of this contamination appear to be *chlorinated hydrocarbon sprays* and/or their vehicles, believed to occur as a result of feeding *sprayed forage* and/or the common practice of *spraying herds for insect control.*

As might be expected, there are considerable variations in the effects of different sources of these meats. In the majority of instances, these reactions may be avoided or greatly reduced by cutting off all fat prior to cooking. Nevertheless, a few patients, otherwise avoiding sources of chemical exposures, still react to beef or lamb from which the fat had been removed as far as possible, but are able to eat the same meat known not to have been chemically contaminated. Others, as might be expected, are actually susceptible to one of these foods *per se,* as judged by the ability of samples, known to have been relatively *uncontaminated chemically,* to induce acute test effects. The possibility that patients may be reacting to *other* chemical additives and contaminants of meat and fowl has not been excluded. These will be discussed later.

Fumigant Residues

Several patients known to be susceptible to one or more related chemical exposures have been *able* to eat dates which were relatively uncontaminated chemically but *unable* to eat dates from the *same grove* fumigated with methyl bromide. It is not general knowledge that *Federal regulations* demand that dates be fumigated in this manner before entering interstate commerce. However, it is of particular interest—in view of the well known laxative effect of *dates* and *figs*—that these fruits, relatively free of chemical contaminants, may generally be taken in one- or two-pound lots *without* inducing laxative effects. These observations suggest that the laxative action of certain commercially available fruits, especially dates and figs, lies in their *mandatory additives* rather than in the fruits *per se.* Exception to this statement might include those persons with a specific susceptibility to uncontaminated sources of fruits and manifesting gastrointestinal responses to their ingestion. It should be emphasized that the total effect of commercially available dates, figs and fruits handled similarly is difficult to evaluate because of the common practice of spraying and other techniques involving additional additives.

Commercially available shelled nuts also commonly precipitate acute reactions in some chemically susceptible patients otherwise avoiding major

chemical exposures, whereas the same freshly shelled nuts are often taken with impunity—in the absence of true susceptibility to these uncontaminated foods *per se.*

The same statement holds for commercially available dried peas, beans and lentils, as contrasted to the response of the same patients to those known to have escaped fumigation. Dried fruits are also apt to be fumigated; but since they are also *apt to have been sprayed* and *may have been sulfured,* no attempt has been made as yet to sort out the sources of reactions commonly occurring in chemically susceptible persons. These comments point up the fact that simply buying dried fruits advertised as *unsulfured* does not insure one of an *uncontaminated* source of supply, since the majority of samples also have been sprayed and fumigated!

During the past year ingestion tests have been performed with commercially available sources of wheat and corn; also with samples of these grains grown in the absence of chemical fertilization and additives. Indeed, the farm on which the samples were grown had not had commercially available fertilizers used on it for the past thirty years, and the grains were ground in a stone mill used only for materials originating on this farm.

When parallel ingestion tests were performed with these materials of known cultural and technological pedigree and with unenriched commercially available wheat and with corn meal, a relatively greater number of chemically susceptible patients reacted to the commercial materials. In all instances, these materials were cooked in spring water and salted to taste.

Also, a greater number reacted to commercial corn meal than to commercial cracked wheat cereal, although the incidence of sensitivity to these two cereal grains is approximately the same.[13] This difference may be attributable to the *sulfur treatment* of corn products, which will be discussed later, although both commercially available supplies may have been fumigated in storage.

Bleaches

Bleaching agents (oxides of nitrogen, chlorine and benzoyl peroxide) employed in whitening flour have not been separated from other potential sources of chemical contamination of wheat. Clinical responses attributable to eating of white bread cannot be interpreted as incriminating bleached flour because of the host of *other additives* of *chemical origin* entering the current manufacture of bread.

Sulfur

It is also difficult to evaluate clinical effects apparently arising from the treatment of foods with sulfur because of the multiplicity of other possible contaminants as well as existence of susceptibility to the uncontaminated food *per se.* Nevertheless, the several times that this has been attempted in individuals having aspects of the chemical problem, leaves the impression that *sulfur is a major chemical contaminant* of the food supply.

In the course of performing ingestion tests with peaches dusted with sulfur but otherwise uncontaminated, several test subjects reacted acutely to the sulfured peaches. The most acute reaction occurred in a woman who had failed to react to uncontaminated peaches. Twenty minutes following the ingestion of a sulfured peach she complained of nervousness and tenseness with alternating chilling and sweating sensations. She became nauseated at thirty minutes; vomited a part of the peach at thirty-five minutes. At forty minutes she remained cold, clammy, pale and depressed. Despite pumping her stomach contents, she continued to manifest severe abdominal cramps, residual aching, fatigue and depression for the remainder of the day.

A few patients have inquired why they were unable to eat French fried potatoes in restaurants, whereas home French fried potatoes were taken without trouble. Investigation revealed the almost universal practice of larger restaurants to purchase peeled and sliced potatoes for French frying which had been dipped in a *solution of sulfur dioxide* as an anti-browning measure. The same routine may be employed in the manufacture of potato chips and in handling freshly cut apples and peaches.

Dried fruits are commonly treated with sulfur, as previously mentioned. Some *fresh* fruits and vegetables, notably asparagus, are blanched with solutions containing sulfur dioxide.

The processing of corn begins with soaking of the whole kernels in sulfur dioxide solution. Although this practice avoids fermentation while the physical parts of the kernels are separated, it apparently imparts a sulfur contamination to all manufactured corn products. These include cornstarch, corn flour, corn sugar (dextrose and glucose), corn oil and corn-derived dextrins. Sulfur is also commonly employed in the manufacture of cane and beet sugar.

Artificial Colors

The addition of artificial colors (coal-tar dyes) to foods—permitted by Federal regulations—appears to be another major source of clinical reactions in highly susceptible patients otherwise avoiding major sources of chemical additives and contaminants.

To be certain that these reactions were attributable to dyes and not to other additives or to the food as such, three patients, giving this history and also highly susceptible to other chemical additives, ingested in spring water the amount of dye (Amaranth No. 2) calculated to have been present in a large serving of colored gelatin. Two of the subjects developed severe reactions when tested blindly to this material.

Artificially colored citrus fruit has also been strongly suspected in this group of patients, but this possible source of chemical contamination of fresh fruit has not been separated from the potentiality of contamination arising from the fungicide treatment of citrus crates. The additional factors of

sweetening agents and canning processes must also be considered in interpreting reactions to canned citrus juices.

Several patients in this group under discussion have reported unquestionable reactions after eating dyed sweet potatoes, whereas *undyed* sweet potatoes or dyed ones may be used if carefully peeled. As a practical point, the common practice of dying sweet potatoes may usually be detected by noting the presence of dye on the broken ends of tubers. Similar reactions have been traced to the increasing practice of dying white potatoes red. A listing of other commercially colored foods will be given in the summary.

Individuals known to be highly susceptible to and avoiding other incriminated chemical exposures may react, either acutely or chronically, to artificially colored foods and drinks. The most sharp reactions have occurred to the presence of coal-tar dyes in imitation fruit drinks and in alcoholic beverages.

For instance, food diary evidence correlated the ingestion of an artificially colored grape flavored soft drink with epileptiform seizures in a fifteen-year-old boy. Individual food ingestion tests with chemically uncontaminated grapes, commercial grapejuice and various sugars failed to react, but the trial ingestion of the suspected soft drink precipitated a typical attack. It should be mentioned, however, that this beverage also contained a chemical preservative and that the subject was aware of the identity of the test material. Avoidance of the major sources of chemically contaminated foods and other major chemical exposures relieved both his seizures and chronic fatigue. Several other patients, including the first case report of this article, have reacted acutely to the ingestion of alcoholic beverages containing coal-tar colors.

Artificial Sweeteners

Although many chemically susceptible patients have reported reactions to saccharine and Sucaryl and claim to profit by their *avoidance,* neither has as yet been subjected to controlled conditions of testing.

Foods Exposed to Gas

Most bananas are artificially ripened by exposure to ethylene gas immediately before their distribution in retail markets. The longer the interim after this exposure, the more readily bananas are tolerated by those highly suspectible to chemical exposures. This variability probably accounts for the fact that chemically susceptible patients sometimes seem to react to bananas and at other times seem able to eat them without apparent trouble. Naturally ripened bananas may sometimes be differentiated from gassed bananas by their black seeds and small speckled spots on their skins, in contrast to white seeds and large blackened areas of the skin at points where gassed bananas had been bruised in handling or shipping.

Certain other fruits are sometimes stored in the presence of ethylene and other gasses. But since the buyer usually is unaware of this possible

source of contamination and since most fruits are contaminated in various other ways, this exposure has not been subjected to controlled testing.

Certain individuals of this group under consideration are also apparently susceptible to coffee. Although many are truly coffee sensitive, as determined by the ingestion of electrically roasted coffee, some are able to drink electrically roasted coffee but react to gas roasted coffee. How commonly the universal practice of roasting coffee over a gas flame contributes to the extraordinarily high incidence of apparent sensitivity to coffee has not been investigated statistically.

In 1950, the writer reported six cases of apparent sensitivity to cane, as determined by performing individual ingestion tests with granulated cane sugar.[34] But as the chemical additive and contaminant problem later unfurled, it was subsequently learned that each of these patients was also highly susceptible to various chemical exposures. This observation initiated an investigation of the possible ways in which cane sugar might be contaminated chemically. The major source of chemical contamination is believed to occur in the *process of clarification* of the cane syrup as it is filtered through bone char. From time to time, these filters are washed, dried and reactivated at 1,000 degrees over a gas-fired flame. The char is believed to absorb the products of combustion of the gas and to impart these contaminants to subsequent filtrates.

In order to check this hypothesis, several subjects with *other* aspects of the chemical susceptibility problem and having apparent reactions to cane, failed to react when tested blindly with a special lot of cane sugar which was manufactured by means of a process by-passing bone char filtration. However, a few individuals have been observed subsequently who are apparently susceptible to cane as such, since they manifest unmistakable clinical symptoms after taking either of the above samples.

The manufacture of beet and corn sugar often involves similar processes.

Containers

The possibility that foods may be chemically contaminated by plastic wrappers and other containers is also difficult to evaluate because of the range of materials employed for this purpose and the difficulty of sorting out this possible source of contamination from others. However, there is no doubt that such chemical contamination may exist.

The writer has unmistakable evidence indicating chemical contamination of food stored in covered plastic freezer dishes, whereas the same lot of fresh food has been taken by the same person without reaction. A few extraordinarily susceptible persons have apparently reacted to foods stored in open glass containers in plastic lined refrigerators. This type of reaction is reduced or eliminated by storage of food in tightly fitted glass dishes. Unfortunately, enamel-lined refrigerators and deep freezers are no longer manufactured.

Generally speaking, the more flexible and odorous the plastic, the more

it is apt to contaminate the food in which it is wrapped. Also, the longer the food remains in such a container and the more liquid or intimate the phase of contact, the more likely chemical contamination is to occur. Lee[35] pointed out that if a given wrapper may be filed without the development of an odor, it probably is not a significant factor in contaminating the food with which it is in contact. This important subject deserves a more thorough investigation in patients known to be susceptible to various other aspects of the chemical environment.

Citrus fruit is commonly packed in crates impregnated with a fungicide. Although this possible source is strongly suspected and has been incriminated as an *inhalant,* it has not been incriminated as an *ingestant* because of the difficulty of obtaining unsprayed and undyed citrus fruit packed in this manner. The odor of the presence of a peck of citrus fruit which had been packed in a diphenol impregnated case in the home of a patient with this clinical problem has been incriminated. Respiratory symptoms developed each time this person entered the portion of her home where these oranges were stored. Her husband then washed each orange in hot soapy water, brushing each fruit separately, but the odor still lingered and continued to cause acute respiratory symptoms. Somewhat later, this patient became acutely ill and was confined to her bed during the process of moving with the complaints of asthma and headache. Her husband then recalled that her asthma had started shortly after packing cases had been brought into the home. Her symptoms subsided after the citrus packing boxes had been removed but recurred when the same boxes were brought back into the home without the subject's knowledge. This patient also becomes chronically depressed after eating commercially available oranges regularly, but is able to eat with impunity oranges known not to have been sprayed, dyed or packed in fungicide-treated cartons.

It should also be pointed out that packing cases and express cars once contaminated with DDT and similarly acting chlorinated hydrocarbon insecticides retain this contamination for long periods and may subsequently contaminate other loads. This type of chemical contamination may explain the unusual patient who is able to use naturally grown wheat which is transported from the producer in sealed milk cans but not the same wheat which is packaged in paper or cardboard and shipped several hundred miles by express. This type of chemical contamination underscores the desirability of having local sources of produce which may be transferred directly from producer to consumer without the necessity of passing through the usual commercial channels.

The observation that certain patients, susceptible to other chemical additives and contaminants, reacted to foods canned in lined tins but not to the same raw or uncanned food prompted an investigation of the possible contaminating significance of can linings. This problem was difficult to study because of the fact that many fruits and vegetables were also sprayed or contaminated by other processes prior to canning. Consequently, obser-

vations were limited to salmon canned in glass as contrasted with salmon canned in tins having the usual golden-brown inner linings, and with garden fresh tomatoes of known cultural pedigree as compared with commercial tomatoes canned in lined and unlined tins. When these foods were given to selected patients, otherwise avoiding chemical additives and contaminants to which they were known to be suspectible, *acute reactions* to salmon and tomato canned in lined tins occurred.

Reactions failed to occur to the same foods canned in glass, to *fresh* salmon or tomatoes, or to tomatoes canned in *unlined* tins. Although the opportunity was not present to test identical sources of salmon and tomato prior to and following canning in metal, the group of patients under investigation have been able to eat fresh salmon or frozen fresh salmon (*i.e.*, the intact fish) and field-ripened tomatoes without apparent trouble. This type of evidence and the continued observations of many patients suggest that the phenolic resins and related materials most commonly entering the manufacture of can linings presumably contaminate the contents of the can. Owing to the well-known volatility of phenolic compounds, it appears that such materials are also at least in part responsible for the characteristic differences in taste between such items as tinned versus untinned salmon, peaches, and certain other foods almost invariably canned in heavily lined tins.

Once this major source of food contamination by means of chemicals was recognized, the additional *avoidance* of foods canned in this manner by certain persons highly susceptible to other chemical exposures has resulted in the relief of their residual chronic symptoms.

Waxes

Certain foods waxed with a heavy coating of paraffin, such as rutabagas and parsnips, also have been shown to cause acute symptoms in certain patients highly susceptible to chemical exposures and otherwise avoiding them. Wax particles adhere to cut surfaces in the ordinary process of peeling such waxed vegetables. This may be demonstrated by immersing a previously waxed and peeled root in boiling water. Under such circumstances wax droplets rise to the top of the water as contrasted to the similar immersion of the same *unwaxed* peeled vegetable used as a control. Although these reactions are believed to be attributable to the waxing process and the adherence of wax particles to the vegetable, the opportunity of testing the same lot of vegetables prior to and following waxing has not been present.

Cucumbers, green peppers and certain fruits are commonly waxed more lightly and polished. Their ingestion has also been followed by acute *reactions* in this type of patient whereas the same vegetables of known cultural pedigree have been eaten without trouble. Although peeling a waxed cucumber apparently avoids this source of chemical contamination, peeling a green pepper is less feasible. Peeling an apple may also eliminate this

source but, as previously described, it is ineffective in counteracting spray residues which apparently penetrate the entire fruit.

Glycols

Although a few patients have reported reactions to foods containing added glycols, especially certain dry cereal products and prepared cocoanut, a detailed study of this possible source of food contamination has not been made.

Antibiotics and Hormones

There are many potential sources of chemical contamination of meat, poultry and fish. These include the common practice of implanting synthetic hormones (usually stilbestrol) in the flesh of the animal and feeding antibiotics and tranquilizers. The latter seems to be an increasingly common practice in the shipment immediately prior to slaughter. There is also the officially approved practice of dipping chicken and certain other fowl in antibiotic solutions, as well as the addition of coal-tar dyes and certain other chemical agents in the processing of meats.

As a result of this profusion of potential chemical contamination in the production of meat and fowl, it has only been possible to differentiate between commercially available sources of these foods, on the one hand, as against the same foods of known cultural and technological pedigree, on the other. The fact remains that many patients presenting aspects of the chemical susceptibility problem as described and otherwise avoiding incriminated sources of these contaminants react to most sources of commercially available meat and poultry. Unless a true food susceptibility exists, these same patients are able to eat the same foods known to have been grown and processed in the absence of the above-mentioned techniques and in the absence of the animals having been fed sprayed forage or otherwise treated with chemical insecticide-oil mixtures for insect control.

Many of the same group of patients have observed that they are able to eat fresh fish or that frozen in *large* pieces and sawed into smaller portions while still frozen, whereas they react to the same fish which was frozen in pound lots. One wonders if this is not due to the permissible practice of dipping fish in *antibiotic solutions*—there being a much larger surface available for chemical contamination under these circumstances.

Miscellaneous

The possibility that *chemical preservatives* of foods may be major sources of reactions in persons known to be susceptible to other facets of the chemical environment is urgently in need of study. Although evidence which incriminated preservatives in foods has existed in several instances—sufficient to cause patients to abstain voluntarily from such foods—multiple chemical exposures have almost always been involved.

The possible deleterious effects of foods grown on chemically fertilized soils shown to be contaminated as a result of the repeated application of potent chemical mixtures for the abatement of insects and weeds, or both, have not been investigated.

To be certain that such factors were *not* operating as additional sources of chemical contaminants, the chemically less-contaminated foods used as controls were obtained from so-called "organic" farms in which approved practices had been employed for several previous years. Although this has encouraged so-called organic plant culture for food purposes or for the feeding of animals later to be used as human food, this is not to be taken either as a blanket indictment of other practices or as a blanket endorsement of what is usually referred to as organic farming and gardening. Indeed, certain farmers who advertise their produce as *organically grown* regularly employ insecticide sprays, fumigation (sometimes required by law) and certain other practices that have been *incriminated* in the investigation of certain patients known to be highly susceptible to a wide range of chemical excitants.

Consequently, in the present unsatisfactory state of agricultural affairs —as far as the chemical environment is concerned—only those individual producers are currently recommended whose foods have consistently been tolerated by a large group of these diagnosed and controlled patients. This has usually entailed a visit to such farms and, in certain instances where a question of doubt exists as to the practices actually employed, valuable information has been obtained by interviewing a given farmer's neighbors.

The economic pressures to employ chemical practices in agriculture which insure against loss, improve the appearance, yield and keeping qualities of produce are so great that reliable producers sometimes *deviate from their former practices.* Several such instances have been uncovered. The only way in which this has been accomplished to date has been by the report of several correctly diagnosed and controlled patients suspecting a given source of supply. When such cases are investigated, the cause of the chemical contamination usually has been uncovered.

Because of these various factors increasing the costs of food production, persons demanding chemically less-contaminated foods should be prepared to pay premium prices for this type of quality.

SUMMARY

These observations—although preliminary and far from complete—emphasize several important points:

1. Chemical contamination of a given food often occurs as a result of multiple cultural and processing techniques. The significance of any given procedure may be determined only when it has been separated from *other* potentially contaminating processes.

2. The role of any given chemical food contaminant may best be

appraised by observations in patients who are known to manifest other aspects of the clinical problem of susceptibility to chemical additives and contaminants, at a time when other such exposures are avoided and the individual is symptom-free.

3. The possibility that a true susceptibility may *exist* to the chemically uncontaminated form of *any* food is always present and further complicates the detection of reactions to chemical additives and contaminants.

These points underscore the following statement: To evaluate the role of a given chemical food contaminant on health and to *differentiate these effects* from other co-existing chemical contaminants and from food allergy *per se* requires the presence of: (1) Food sources of known cultural and processing pedigree; (2) Specifically diagnosed patients in respect to their demonstrated susceptibility to chemical exposures and specific foods; and (3) A knowledge of the dynamic nature of both processes.

For instance, clearest test results are obtained in chemically susceptible patients who have been avoiding all known sources of chemical additives and contaminants of their environment for several days prior to these experimental exposures. Susceptibility to chemically uncontaminated foods is likewise best demonstrated by a test re-exposure in a person who had previously been regularly exposed but who has been avoiding the food in question for a period of several days prior to such a test.[13,16] In other words, testing for *chemical contaminants of food* and *foods per se* should be attempted in a *non-adapted phase* in order to demonstrate the presence of diagnostically significant acute reactions.

B. WATER ADDITIVES AND CONTAMINANTS

Chlorine

Watson and Kibler[36] were apparently the first to demonstrate the existence of susceptibility to chlorinated water. Chlorination of the water supply is such a common cause of chronic symptoms of the type described in patients susceptible to other facets of the chemical environment that it must be tested for in all instances if such exposures exist. This is best accomplished by the use of spring water during periods of comprehensive environmental control, and then returning to the former chlorinated water supply. Although testing commonly has to be done with water that is both chlorinated and fluoridated, cases in which this combination has been incriminated usually have observed reactions from drinking water which had been chlorinated only.

Some patients, in whom the susceptibility has been of lesser degree, have been able to drink boiled chlorinated drinking water whereas unboiled drinking water was not tolerated. Presumably this is the result of the chlorine being highly volatile.

Certain persons with advanced susceptibility to the chemical environment react quickly to attempts to swim in chlorinated pools, whereas no difficulty is experienced when swimming in natural waters. A few have

reacted to the inhalation of the odors of indoor chlorinated swimming pools, as previously noted.

Fluorine

The possible effects of fluoridation of drinking water have not been studied by the writer, since the water supply of this area is both chlorinated and fluoridated, and non-chlorinated-fluoridated water from the same source is not readily available for test purposes. Neither has the possibility of certain other additives to the water supply been investigated.

The use of chlorinated-fluoridated water for washing foods does not ordinarily cause symptoms even in the most highly susceptible, but permitting foods to *stand* in this water prior to cooking has been incriminated in several cases. Also, inhalation of the steam of boiling chlorinated-fluoridated water in cooking, or from running a hot tub in a closed bathroom, or from steam radiators, has been demonstrated as the cause of symptoms in certain highly susceptible persons.

Softened Water

The tendency to soften *all water* entering the kitchen is one of the built-in potential hazards of present-day home construction. Although this water treatment apparently may be tolerated by many, a minority may become highly susceptible to it and be made unexplainably ill by it. Whereas softened water may be used with advantage for all other purposes, *unsoftened* water should be available for *drinking and cooking*. This simply means having an extra tap in the kitchen. The positive correlation of *longevity* with hardness of the water supply is of interest in this connection.[37]

C. BIOLOGICAL DRUGS

Preservatives

One of the causes of reactions to repeated doses of allergenic extracts is the existence of susceptibility to the chemical preservatives in such biological materials. This was observed independently by Glaser[38] and the writer.[5]

This usually manifests with the gradual onset of bizarre reactions—either local or constitutional in type—often several months or years after the onset of injection therapy. Such reactions persist to about the same degree or increase despite repeated reductions in the potency of the active ingredients. This interpretation of reactions is established by their presence from the injection of phenol-containing diluent and their absence following the injection of phenol-free extracts containing the same dose of active principles.

Several patients, known to have been highly susceptible to other facets of the chemical problem, have developed constitutional symptoms following intradermal skin tests with phenol-containing extracts. The most extreme instance of this type observed was that of rapidly progressive headache, nausea, dizziness and faintness immediately following four intradermal injections to which there was no *local* reaction. Identical responses occurred

each subsequent time that phenol-containing extracts were employed but not when phenol-free extracts were used, both having been injected blindly as far as the patient was concerned.

Because of the frequency of reactions to phenol in this group of patients, it has been necessary to maintain a set of phenol-free allergenic extracts for the past several years. A satisfactory preservative has not been found as yet; both Zephirin and Merthiolate not only were associated with occasional reactions, but in the concentrations used permitted mold growth. Preservative-free allergenic extracts have the obvious disadvantage of needing to be replaced frequently and requiring bacteriologic techniques in handling.

Reactions to the injection of liver extract, insulin, epinephrine and certain other biological extracts containing chemical preservatives may also be traced to the *preservatives*. But, since either the active principles, excipients[39] or preservatives may be incriminated as causes of such drug reactions, it is often exceedingly difficult to be certain that the preservative is involved. Materials, such as epinephrine for instance, are so unstable in the absence of chemical preservatives that they cannot be secured for test purposes.[40]

A few patients, having other facets of the chemical problem, have been observed to develop large local reactions to troublesome general effects from each injection of liver extract, irrespective of the brand, but were able to eat liver either in daily or intermittent amounts. The questions of insulin reactions have not been investigated by the writer in this connection.

It is interesting to speculate that so-called epinephrine-fastness occurring in the continued treatment of bronchial asthma might possibly be explained on the basis of a susceptibility to and development of an addiction-type response to the chemical preservatives of the preparation. Lessening of the immediate beneficial effect of repeated injections as well as the progressive need for more frequent and larger doses suggests such a mechanism.

Dyes

Coal-tar dyes have long been used in drug manufacture. Although this subject has not been studied extensively, the writer has seen a few instances in which the dyes employed in Premarin have apparently been responsible for reactions following maintenance or intermittent dosage of this biological product in individuals highly susceptible to the ingestion of chemical dyes. At least, material supplied by the manufacturer,* known to be free of both chemical dyes and excipients (cornstarch), have been tolerated by these individuals.

Other Materials

The possibility of other sources of chemical contamination of biological drugs cannot be excluded. In addition to preservatives and dyes, these

*Furnished through the courtesy of Ayerst, McKenna & Harrison.

include plastic encapsulating materials, artificial sweeteners and flavors, as well as the source materials as a result of treatment with solvents and many other chemical agents. The incorporation of mineral oil and other synthetically derived materials to delay the absorption of biological extracts requires further observation to evaluate possibilities of reaction, since mineral oil is capable of inducing contact and ingestant reactions.

Part V. Chemical Drugs, Cosmetics and Personal Contacts

In view of the extensive literature dealing with reactions to chemically derived drugs, cosmetics, contact dermatitis and other contactant reactions, these subjects will be presented briefly. The main point to be emphasized here is the interrelationship existing between these reactions and susceptibility to other facets of the chemical environment existing in the same person.

This emphasis on the characteristic overlapping tendency and multiplicity of response of individuals to various chemical materials has not been brought out by concise one-track case reports or by studies showing the relative incidence of reactions to individual chemical agents. As a consequence, the *reaction-proneness* of certain persons and their tendency to develop new susceptibilities is frequently underestimated.

A. Synthetic Drugs

The tendency toward *multiple reactions* to related materials is nowhere observed more clearly than with reactions to chemical drugs. In fact, this tendency to react to many different drugs is so marked in certain individuals that sharp differences of opinion may arise between such patients—who are suspicious of *all* drugs—and their physicians, who tend to think of drug reactions as independent entities. Because of their proneness to drug reactions from past experiences on the one hand, and the apparent inability of many physicians to understand this apprehension on the other hand, many individuals afflicted in this manner have become increasingly loathe to seek medical care. Indeed, some patients stick tenaciously to a certain physician, not because he has helped them but because he has never made them *worse!*

Physicians need to be more alerted to this proneness to reaction to chemical drugs because of the ease with which such persons may be harmed. The tendency for individuals, already susceptible to certain facets of the chemical environment, to react to chemically derived drugs is shown by the questionnaire evidence in two series of patients. The first series of eighty chemically susceptible patients was studied by means of an early and relatively incomplete form. Approximately 50 per cent of this group were known to react to aspirin, barbiturates and sulfonamides—an extraordinarily high percentage.

The second series of 250 patients selected on the basis of known reactions to one or more facets of the chemical environment were questionnaired by means of a more complete list of drugs. Between one-quarter and one-third of this group claimed to react to aspirin, barbiturates and sulfonamides. These drugs were followed closely by antihistamines, local anesthetics and synthetic vitamins. The relatively lower incidence of reported drug reactions in the latter group is apparently the result of including a larger number of less advanced cases in this series (1958) than in the former (1952). The incidence of reactions to other drugs is shown in the accompanying table.

1952 SERIES		1958 SERIES	
(Total Cases 80)	Per Cent	(Total Cases 250)	Per Cent
Aspirin	38 — 47.5		77 — 30.8
Barbiturates	36 — 45.0		60 — 24.0
Sulfonamides	42 — 52.5		59 — 23.6
Antihistamines	30 — 37.5		56 — 22.4
Novocaine	13 — 18.7		56 — 22.4
Vitamins	24 — 30.0		39 — 15.6
Benzedrine	17 — 21.2		25 — 10.0
Demerol	11 — 13.7		24 — 9.6
Pentothal			17 — 6.8
Diodrast			14 — 5.6
Phenolphthalein			12 — 4.8
Privine			9 — 3.6
Stilbestrol			8 — 3.2
Amidopyrine			8 — 3.2
Butesin Picrate			6 — 2.4
Acetanilide			5 — 2.0
Pontocaine			5 — 2.0
Thorazine			4 — 1.6
Dolophine			3 — 1.2
Bromsulphthalein			2 — 0.8
Decholin			2 — 0.8
Diodoquin			2 — 0.8
Diamox			2 — 0.8
Butazolidine			2 — 0.8
Antibuse			2 — 0.8
Furadantin			1 — 0.4

In general, the more advanced and long standing the illness and the more drug therapy the patient has received, the greater the number of synthetic drugs suspected of causing reactions. Moreover, individuals known to be highly susceptible to certain aspects of the chemical environment seem more prone to manifest untoward symptoms to treatment with synthetic drugs. Such reactions also tend to develop after shorter periods of therapy than occur in less susceptible persons or those in the absence of such a history.

A *synthetically derived* substance may cause a reaction in a chemically susceptible person when the same material of *natural origin* is tolerated, despite the two substances having identical *chemical* structures. This point is illustrated by the frequency of clinical reactions to synthetic vitamins—especially vitamins B_1 and C—when these naturally occurring vitamins are tolerated. There is also other evidence indicating that the biological activity of synthetic and natural vitamins is not identical.[41]

Finally, it should be emphasized that these tables showing the relative incidence of reactions to common drugs in highly susceptible patients

consist only of questionnaire evidence. Because of the hazards involved, no attempt was made to confirm these reactions, although several had been confirmed as a result of accidental exposures.

B. COSMETICS AND PERFUMES

As with drugs designed for topical application, reactions in chemically susceptible persons may occur to the active chemical ingredients, their bases, artificial colors, scents, preservatives or other chemical ingredients or contaminants. In view of the number of such possibilities, involving both synthetic and natural ingredients, it is often difficult to trace reactions to the responsible material or materials. At times, *combinations of circumstances* give rise to reactions. For instance, a clinically detectible response may occur only when a given material comes in contact with abraided skin, or to contact plus light exposure, or when combined with various other precipitating factors.

In general, however, as far as the majority of chemically susceptible persons are concerned, the scent of cosmetics is by far the most troublesome feature. Although some are much more susceptible to inhalation or contact with cosmetics and perfumes than others, those susceptible to numerous other facets of the chemical environment seem to be potentially more susceptible to cosmetics and perfumes than those without such a history. The most highly susceptible may be not only unable to wear various cosmetics and perfumes but unable to remain in the presence of others who are wearing them.

From a practical standpoint, this problem usually is handled by the avoidance of *all* perfumes, although a given person may be able to tolerate certain types or brands. Cosmetics and ointments made up entirely of natural ingredients in the absence of artificial colors, scents and preservatives are apt to be tolerated. Unfortunately, these preparations have the disadvantage of not being readily available and often requiring refrigeration.

Problems involved with the personal use of scented soaps, shampoos and various other toilet articles have been discussed earlier.

C. MISCELLANEOUS CONTACTS

The major problems not previously discussed center around reactions to textiles and their finishes, and other plastics.

Textiles and Finishes

In general, the less the odor of textiles and plastics, the less their tendency to cause reactions in chemically susceptible individuals. In this connection, *rayon* and *nylon* seem to cause far less trouble in this group of patients than other woven synthetic fabrics. Many of the contactant type of reactions to synthetic textiles may be due in part—or entirely—to the *finishes* of these materials.[42] Several instances have been observed by the writer in which

unquestionable reactions occurred to *finished nylon products* when the same patient had been able to wear a square yard of *unfinished nylon fabric* pinned to the inner side of his pajamas without evidence of reaction. However, the fact remains that practically all *nylon* garments and hosiery are "finished," although there is considerable variability in the tolerance to these finishes among patients. Some brands may be used by certain patients while others may not.

Cotton goods also may be finished in a manner causing reactions in certain patients of this group. Although cotton materials often are less troublesome *after laundering,* some persons remain highly susceptible to certain cotton fabrics despite repeated washings. These persistent causes of reactions are most commonly attributable to the *plasti-starch treatment* of cottons, especially bed linens.

The effects of plastic-impregnated linens must be carefully differentiated from contamination of fabrics as a result of laundering, for either may induce reactions in chemically susceptible individuals. Certain of these patients have demonstrated reaction to contact with cottons which have been washed with detergents, bleached, or dried in a gas fired drier. Each of these sources of chemical exposure must also be differentiated from each other as well as from contact-type reactions attributable to the cornstarch content of sheeting, which sometimes occurs in individuals who are also highly sensitive to corn.

Aside from contact dermatitis from dyed woolens, the processing of wool does not seem to be a major factor in causing reactions in chemically susceptible persons. However, a true susceptibility to wool, both as a contactant and as an inhalant,[43] is common. Wool, being more *abrasive* than certain other fabrics, may also cause extreme physical irritation of the skin.

Other Plastics

In general, the greater the *odor* and *flexibility* of a plastic, the more likely it is to result in both inhalant and contactant reactions. Although contact-type reactions have been reported to a wide range of plastics, their occurrence in a given group of patients is not as high as might be expected. Occasional instances of contact reactions to prolonged direct contact with formica and vinyl table and counter tops have been noted. Bakelite, of the type formerly employed in the manufacture of telephones, has not been incriminated but the new colored plastic telephones may cause both inhalant and contact type responses.

Plastic jewelry, combs, powder cases, brushes, purses, pencils and pens may cause reactions in this group of patients but only rarely are incriminated as contactants. Prosthetic devices such as spectacle frames, hearing aids and dentures are more apt to be associated with chronic reactions because of the more constant exposures involved. The occasional person who is intolerant to acrylic dentures and plastic fillings presents a particularly

difficult problem. The most satisfactory answer to this problem involving plastic spectacles and dentures is to construct these devices from metals. The question of reaction to other prosthetic devices is too specialized to be considered here.

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(To be concluded in the August issue)

THE AUTHOR'S MOTIVE FOR WRITING

These views, as usual, pleased some more, others less; some chid and calumniated me, and laid it to me as a crime that I had dared to depart from the precepts and opinion of all anatomists; others desired further explanations of the novelties, which they said were both worthy of consideration, and might perchance be found of signal use. At length, yielding to the requests of my friends, that all might be made participators in my labours, and partly moved by the envy of others, who receiving my views with uncandid minds and understanding them indifferently, have essayed to traduce me publicly. I have been moved to commit these things to the press, in order that all may be enabled to form an opinion both of me and my labours.—WILLIAM HARVEY, 1578-1667. "Anatomical Dissertation, Concerning the Motion of The Heart and Blood in Animals." (From *Moments of Discovery. The Development of Modern Science.* Edited by George Schwartz and Philip W. Bishop, New York, Basic Books, Inc., 1958.)

President's Letter

If this report may begin with a personal note, I would like to express my sincere appreciation for the great honor that the members have accorded me in electing me to the chief executive position of The American College of Allergists.

As with many comparable societies, the continuing activities of the College culminate in the annual meeting. Few members realize how much effort on the part of so many individuals is involved in arranging a convention. The glowing comments about the Dallas meeting in March constitute a compliment to all those who made it possible. Special thanks are due to the Committee on the Instructional Course, the six sectional chairmen, the chairmen of the standing committees, the Local Committee on Arrangements, the committees of the Women's Auxiliary, the Executive Vice President and the Treasurer. All these, not to mention the instructors, speakers, panelists and discussants, deserve the credit for the high scientific level of the presentations, the educational value of the Instructional Course, the eminent sociability, and the excellent physical arrangements of the meeting just past. We are also indebted to our Exhibitors and Sponsors, without whose support our annual conclave would not be feasible. And our appreciation also includes the Schering Corporation for sponsoring the superb Social Hour preceding the banquet.

Now, to look to the future. The Eighteenth Annual Congress will be held on April 4, 5 and 6, 1962, and the Graduate Instructional Course on April 1, 2 and 3, 1962, at the Hotel Radisson, Minneapolis, Minnesota. I am informed that the hotel has been completely refurbished and offers unmatched facilities for our purposes.

It is none too soon to begin to plan, not only to attend the 1962 session, but also to deliver a paper or present a scientific exhibit. The over-all program chairman will be Mayer A. Green, M.D., 6111 Jenkins Arcade Building, Pittsburgh 22, Pennsylvania. Dr. Giles A. Koelsche has kindly consented to act as Program Consultant.

Fellows wishing to appear on the program should send abstracts of their papers to Dr. Green. These must be submitted in quadruplicate, be limited to 250 to 300 words, and be accompanied by a 35 to 40 word résumé-summary for inclusion in the printed program, if accepted. To be considered, papers must be received before November 15, 1961, but should be submitted as soon as possible. In accordance with a resolution of the Board of Regents, no extension of this dead-line will be permitted.

Associate Fellows of the College are particularly urged to submit papers in competition for the Bela Schick Award granted annually through the generosity of the Women's Auxiliary. The instructions for these are the same, but the essayist should also mention that the abstract is in competition for this Award.

For several reasons, your officers are especially desirous of reviving competition for the Clemens von Pirquet Award, which is a prize of $250

and a Certificate of Award, presented to the Intern, Resident or Medical Student submitting the best paper on any aspect of allergy or related fields of medicine. To encourage this, the provisions have been changed this year. The entire manuscript (in quaduplicate) should be sent to Dr. Green before November 15, 1961. The winning essayist will be notified well before the convention and will be invited to attend, but need not be present in person to receive the Award. All our members are requested to stimulate the interest of the interns, residents and medical students with whom they are in contact, to compete for this Award.

Fellows, Associate Fellows and non-members (as available space permits) wishing to display scientific exhibits April 3 to 5, 1962, should send brief summaries and descriptions (in duplicate) to the over-all chairman before December 15, 1961.

I am happy to announce that Lowell L. Henderson, M.D., Rochester, Minnesota, will be Chairman of the Graduate Instructional Course. An effort is being made to obtain accreditation by the American Academy of General Practice. Plans for the Course are already well-advanced; a new and distinctive "format" is being adopted, and it promises to be the finest ever.

The chairmen of the six Sectional Meetings to take place on April 6, 1962, will be Frederic Speer, M.D., Kansas City, Kansas, for Allergy of the Nervous System; Maurice C. Barnes, M.D., Waco, Texas, for Dermatologic Allergy; Leland H. Prewitt, M.D., Ottumwa, Iowa, for Ophtho-Otolaryngologic Allergy; Howard G. Rapaport, M.D., New York City, for Pediatric Allergy; Bennett Kraft. M.D., Indianapolis, Indiana, for Psychosomatic Allergy; and Stephen D. Lockey, M.D., Lancaster, Pennsylvania, for Technology. These chairmen would be happy to hear from members of their respective sections regarding suggestions for their programs.

The Women's Auxiliary has requested that we announce that they are again generously underwriting several scholarships to the Graduate Instructional Course in Allergy in 1962. The scholarships will be awarded on the basis of merit and in accordance with the order in which the applications are received. Physicians wishing to be considered should send their applications to Dr. Mayer A. Green. In the case of Interns and Residents, the application should be accompanied by a letter of approval from the Medical Director or a comparable official of the hospital at which they are serving.

The undersigned would appreciate receiving from those chairmen of standing committees who have not already done so, suggestions for the appointment of their committee members.

Your officers stand ready to serve you. All members of the College are asked to communicate with us at any time regarding College affairs and are called on to help make the forthcoming Annual Congress and Graduate Instructional Course in Minneapolis in 1962 an outstanding scientific and social success.

PHILIP M. GOTTLIEB, M.D.
President, The American College of Allergists

Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

SNAKEBITES

Only during a course in immunology is the allergist likely to hear about the medical aspects of the bites of poisonous snakes. At that time, whatever he learns concerning the antigenic properties of snake poisons and the therapeutic use of the antibodies against the agents in the form of antitoxin, is not within the immediate scope of his interest. It may, therefore, be worthwhile to acquaint the readers of this journal with some of the results of recent interesting work by Parrish and his co-workers. This material may be of occasional practical value to the allergist because poisonous snakes are found in almost every state of the Union and medical emergencies caused by bites are by no means rare. Such bites are estimated to number between 2,000 and 3,000 yearly in the United States alone.

Among the numerous groups of people who handle poisonous snakes regularly are herpetologists, biologists and religious faddists. Others, such as people working in forests, are frequently exposed. Thus, repeated experience with bites is not entirely uncommon. A study of such people in Florida showed that an old tenet concerning snake bites needed considerable modification. It is *not* true that snake bites leave a considerable degree of immunity. In fact, increased resistance is uncertain and, at best, of short duration.

Moreover, repeated exposure may result in sensitization rather than immunity. In at least three cases, evidence was secured of allergic sensitization by clinical symptoms and the demonstration of direct and passively transferred dermal sensitization. The poisons of the two members of the genus of pit vipers, the rattle and the moccasin snakes, showed cross-reaction in dermal tests. Parrish suspects that anaphylactic reaction may play an important part in severe reactions after repeated bites and that the subsequent opportunity for effective therapeutic action may have been missed on occasion.

Prolonged contact with dried snake poisons produced allergic symptoms of the respiratory system.

Finally, victims of snake bite may experience an allergic response to horse serum introduced therapeutically in the form of antitoxin.

AJW

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Three cases of liver damage, severe in degree, appeared during treatment with iproniazid. The relationship between its administration and liver disease are discussed.

Anderson, P. C. and Fleck, R. L.: Drug eruption due to Fumagillin complicated by trichophytosis. A.M.A. Arch. Dermat., 77:720 (June) 1958.

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Gregoire, Fernand: The treatment of cough by a non-narcotic antitussive. Canad. Med. Assn. J., 79:180, 1958.

For cough induced by acetylcholine spray, benzonstate, Ciba (Tessalon) was effective as it was also in twenty-six of twenty-eight patients with chronic cough due to tuberculosis.

Gangarosa, E. J., Johnson, T. R. and Ramos, H. S.: Ristocetin-induced thrombocytopenia: site and mechanism of action. A.M.A. Arch. Internal Med., 105:83 (Jan.) 1960.

Ristocetin possesses a direct toxic effect on platelets.

Gallagher, C. H.: The mechanism of action of hydrocortisone on mitochondrial metabolism. Biochem. J., 74:38 (Jan.) 1960.

It appears that oxidative enzymes are inhibited because the permeability of the mitochondria is increased and loss of soluble co-factors occur following administration of hydrocortisone.

Dennis, J. L., Palmer, W. M. and Cleveland, R. W.: Bronchiolitis in infants. J.A.-M.A., 172:688 (Feb. 13) 1960.

Although many asthmatic children have in the past suffered from bronchiolitis in infancy, a single infection may not lead to the development of bronchial asthma.

Demis, D. J., Davis, M. J. and Lawler, J. C.: A study of the cutaneous effects of serotonin. J. Invest. Dermatol., 34:43 (Jan.) 1960.

None of the known serotonin antagonists modify the cutaneous response to the intracutaneous administration of serotonin which is followed by local erythema, a flare and constriction of the larger subcutaneous veins. There is no pruritus but some subjects complained of pain in the inflamed area of the skin. Cyanosis developed in one-fourth of the subjects.

Joyce, C. R. B.: Consistent differences in individual reactions to drugs and dummies. Brit. J. Pharmacol., 14:512 (Dec.) 1959.

Behavioral tests were used in an attempt to separate placebo reactors. Studies of healthy medical students demonstrated that there are significantly different scores.

Simon, S. W.: Symptomatic treatment of asthmatic bronchitis. J. Am. Geriat. Soc., 8:107 (Feb.) 1960.

In a study comprising forty-five patients, it was shown that the addition of dihydrocodeinone to a bronchodilating type of cough mixture did not reduce the frequency or the severity of the cough. There was also apparently no expectorant activity as shown by changes in amount, consistency or effort of raising phlegm.

Sherwin, A. L., Wait, R. H., and Cooper, B. A.: Megaloblastic anaemia associated with phenobarbital therapy. Can. Med. Assoc. J., 82:368 (Feb. 13) 1960.

The use of phenobarbital was continued and a remission of the anemia was obtained by administration of folic acid. Antibiotic agents were administered for the treatment of an acute infection.

Rabinowitz, H. and Halpern, S. R.: Drug allergy in pediatric practice. J. Pediat., 56:75 (Jan.) 1960.

Increasing importance of allergic reactions to drugs is emphasized.

Waugh, W. H. and Metts, J. C., Jr.: Severe extrapyramidal motor activity induced by prochlorperazine. New Engl. J. Med., 262:353 (Feb. 18)1960.

The intravenous administration of Benadryl promptly relieved the laryngospasm and respiratory distress, life-threatening and severity, following administration of prochlorperazine.

Crichton, J. U. and McLean, W. N.: Poisoning due to a commonly used cough mixture intentionally administered. Alberta Med. Bull., 25:15 (Feb.) 1960.

Toxic effects, bizarre in nature, followed the use of Benylin expectorant administered to an infant six-months of age as part of the treatment of a bronchopneumonia.

Dordick, J. R. and Norman, A.: Gastro-intestinal disturbances in association with methylprednisolone (medrol) therapy: preliminary observations. J. Am. Geriat. Soc., 8:116 (Feb.) 1960.

Although two ulcers of the duodenal type occurred following the use of methylprednisolone therapy in patients afflicted with rheumatoid arthritis, the authors suggest that further studies are needed to prove a causal relationship.

PAPERS OF INTEREST

Sanyal, R. K.: Histamine sensitivity in children after pertussis infection. Nature, 195:537 (Feb. 20) 1960.

Rats and mice infected with Haemophilus pertussis become hypersensitive to histamine. Similar hypersensitivity is present in humans, and especially in children. It is not as yet known whether such children are also otherwise allergic.

Fitzgerald, E. W., Jr.: Fatal glomerulonephritis complicating allergic purpura due to chlorothiazide. A.M.A. Arch. Internal Med., 105:305 (Feb.) 1960.

The first reported case of chlorothiazide-induced fatal glomerulonephritis, of which the pathophysiology was suggestive of an allergic-type of response.

Misra, S. S. and Teotia, S. P. S.: Hepatic coma precipitated by chlorothiazide in hepatic cirrhosis with ascites. Lancet, 1:464 (Feb. 27) 1960.

Among twelve patients afflicted with cirrhosis and ascites, the administration of chlorothiazide produced, in four, hepatic coma, reversible by potassium chloride administered in oral doses of 4 grams daily.

Heyck, H.: Serotonin antagonists in management of migraine and Bing's erythroprosopalgia or Horton's syndrome, Schweiz. med. Wchnschr., 99:203 (Feb. 27) 1960.

When a serotonin antagonist 1-methyl-D-lysergic acid-butanolamide-tartrate is administered prophylactically, the number of attacks of migraine suffered by the patients studied occurred less often and were mild. Therapeutically the drug was ineffective. In the eight patients afflicted with histaminic cephalalgia, it was therapeutically effective.

World Health Organization: Hidden contact with penicillin. Bull. World Health Organ., 21:703, 1959.

Lists the four sources of penicillin as: milk, contaminated syringes, virus vaccines and contaminated air. Should have listed penicillin as the contaminant of other antibiotic agents.

Wolf, S.: The pharmacology of placebos. Pharmacol. Revs., 11:689 (Dec.) 1959.

Emphasizes the importance of the properties and potency of placebo-responses in any study of therapeutics.

Fearnley, G. R., Ferguson, J., Chakrabarti, R. and Vincent, C. T.: Effect of beer on blood fibrinolytic activity. Lancet, 1:184 (Jan. 23) 1960.

In two subjects, blood fibrinolytic activity was decreased by beer, cider and white wine, and not changed by the ingestion of whiskey, gin, or absolute alcohol. In the second group of fourteen subjects, blood fibrinolytic activity was lowered two hours after the ingestion of one pint of bottled beer, while that of another four subjects was not changed.

Shanker, A., Bhargava, R. K. and Shrivastava, B. N.: Diethylcarbamazine in tropical eosinophilia. Brit. Med. J., 1:100 (Jan.) 1960.

Diethylcarbamazine administered by the oral route is reported as equal in therapeutic efficiency to arsenic. It is not effective parenterally, as are arsenic preparations.

Guth, P. S.: Kinins produced from bovine colostrum by kallikrein and saliva. Brit. J. Pharmacol., 14:549 (Dec.) 1959.

When bovine colostrum is incubated with urinary kallikrein or calf saliva, substances termed urine-colostrokinin, and saliva-colostrokinin are produced. These are not identical to kallidin, Slow-Reacting Substance A, and other smooth muscle activating agents, yet similarly stimulate smooth muscle.

Tyler, J. M.: The effect of progesterone on the respiration of patients with emphysema and hypercapnia. J. Clin. Invest., 39:34 (Jan.) 1960.

In patients afflicted with emphysema and whose hypercapnia is stabilized, hyperventilation and lowered pCO_2 are produced by progesterone. Those compounds which possess progestational properties, of themselves do not cause such effects, suggesting the presence of fractions which cause this specific reaction.

Beierwaltes, W. H.: What radioisotopes can do for the physician. Postgrad. Med., 27:71 (Jan.) 1960.

The radioisotopes in most common use and the criteria for use of the most important fourteen.

News Items

POSTGRADUATE COURSE IN IMMUNOLOGY, HYPERSENSITIVITY AND PULMONARY FUNCTION

The annual Postgraduate Course in Immunology, Hypersensitivity and Pulmonary Function will be held at Children's Hospital, Washington, D. C., on October 12, 13 and 14, 1961. Additional information may be obtained from Dr. Richard H. Todd, Children's Hospital, Washington, D. C.

BUFFALO ALLERGY SOCIETY

Officers of the Buffalo Allergy Society for 1961-1962 are:

President.....Leonard Wolin, M.D.
Secretary.....Robert Ehrenreich, M.D.
Treasurer.....George Rosenfeld, M.D.

CLEVELAND ALLERGY SOCIETY

Newly elected officers of the Cleveland Allergy Society are:

President.....Frank S. Houser, M.D.
Secretary-Treasurer.....Arthur J. Horesh, M.D.

MICHIGAN ALLERGY SOCIETY

At its annual and final meeting of the year, the Michigan Allergy Society elected the following officers for the year 1961-1962:

President.....Dr. Alex S. Friedlaender, Detroit
President-Elect.....Dr. Hilda M. Hensel, Monroe
Secretary.....Dr. Israel Wiener, Detroit
Treasurer.....Dr. James McLean, Ann Arbor

NEW JERSEY ALLERGY SOCIETY

At the annual meeting of the New Jersey Allergy Society on May 15, 1961, at Atlantic City, the following officers were elected:

President.....Dr. H. W. Diefendorf
Vice President.....Dr. Frank Pflum
Secretary.....Dr. Aaron Weiner
Treasurer.....Dr. Edward Pickert

NEW ENGLAND SOCIETY OF ALLERGY

At the annual meeting of the New England Society of Allergy, the following officers were elected:

President.....Francis H. Chafee, M.D.
Secretary.....Irving W. Bailit, M.D.
Treasurer.....Matthew Derow, M.D.
Councilor.....Hugh Tatlock, M.D.

Book Reviews

THE OFFICE ASSISTANT IN MEDICAL PRACTICE. By Portia M. Frederick and Carol Towner. 407 pages. Philadelphia & London: W. B. Saunders Company, 1960.

Although much of the material in this volume is self-evident, the fact that it is well arranged and can all be found in one text makes it a welcome addition to the library of every physician who employs aides. The book should not be kept in the physician's stacks, however, but rather on a table or desk easily accessible to his assistants who can refer to it often, as they undoubtedly will.

The text, written from a physician's expectations of excellent doctor-patient relations; an efficient examining room procedure; a well run office and a pleasant receiving area, concerns itself with an all-inclusive view of the practice of medicine. Well written, well organized and easily readable, the book contains seventy-five salient illustrations including sample letters, medical histories, office equipment, laboratory equipment and instruments, and positions for physical examinations. Two appendices, one listing suggested readings and reference books for medical assistants; the other, common medical abbreviations and symbols, enhance the general merit and comprehensiveness of the text.

Neither a secretary's handbook nor a nurse's guide, this book may, however, be used by both types of aides, *and* others, as a general reference text to many of the everyday situations of a doctor's office such as a letter declining membership on a civic committee, or the technique of skin testing for an allergy. Some of the most pertinent chapters of the book are concerned with ethics and medico-legal considerations, appointments, medical records and their files, bill collection procedures, physical examinations and office techniques, pharmacology, administration of medications, and library and editorial duties. It will be of interest to allergists to note that an entire chapter is given over to immunology.

Emphasized throughout are the facts that the care, comfort and peace of mind of the patients are the primary considerations of the physician and his staff. Although not used, the word "empathy" could well be substituted for the chapter entitled, "The Right Kind of Reception." The authors continually stress the fact that it is often upon the doctor's staff that the duty of maintaining sincere human relations and good "public relations" falls. Thus a nurse should be able to comfort, without giving a diagnosis, a parent distressed over a child's illness, and a receptionist should be able to divert tactfully a prominent civic leader who has just "dropped in" on one of the doctor's busiest days.

Of particular interest is the point of view (which the authors state is becoming widespread) that positions for women in the medical assistant's field are no longer considered typical "jobs," but rather, interesting "careers."

The authors' approach to the medical assistant's responsibilities is well worth emulating, in that they hope to instill in the physician's aide not just the desire to be well-informed, but the ability to understand fully many of the finer details of medicine and its ancillary disciplines. A pertinent example of this attitude is their concise discussion of the sources and uses of drugs.

With the publication of this text, the authors have successfully met their objectives as quoted in their preface, "To establish higher standards of efficiency among women employed as medical secretaries and assistants, and to inspire these women to render honest, loyal or more efficient service to the profession and to the public which they serve."

BOOK REVIEWS

MEDICAL ALMANAC 1961-62. Compiled by Peter S. Nagan. 528 pages. Philadelphia and London: W. B. Saunders Company, 1961.

The farmer (and the laity in general) no longer has an advantage over the physician by having at his fingertips an incomparable assortment of facts and figures. As aptly stated by Nagan, this volume represents "a compilation of general information, statistics and other data relating to medical care, medical education, medical organizations and literature, incidence of illness and economic aspects of medical practice."

Although small in size, this text is a handy reference for the busy physician who does not have the time to consult his medical texts, journals or encyclopedias for statistics concerning such matters as "injury-frequency rates"; "disabling illness: the twelve diagnoses with the highest annual rates per 1000 population in youth and adult age groups"; "average prevalence of arthritis (diabetes, hernias, peptic ulcers, et cetera) by sex, age and medical attention" and the "number and per cent of edentulous persons by sex and age." Additional copies in a physician's office would be useful for the receptionist, secretary and nurse who are often asked questions of obscure and statistical nature by inquisitive patients.

Of particular value are the lists of "Representative Publications of Departments and Agencies of the Federal Government in Health, Science and Related Fields" and "Medical Schools of the World" including the total enrollment of the latter and the years required for a degree. The table listing the "Reciprocity and Endorsement Policies of Medical Licensing Boards" will undoubtedly be of use to young physicians who are considering moves to other localities.

Examples of the comprehensiveness of this little tome are the statistics on birth rates which have been categorized into the finest divisions so that one can easily find, for example, the "Median Age of Mother by Live-Birth Order and Color," or else the "Registered Live Births by Birth Weight, By Age of Mother and By Sex of Child."

The section on "Medical Manpower" in the United States lists by year the number of medical schools, the number of medical students and the number of graduates from 1810 to date. Also included in this section are the numerical breakdowns, by regions and by states, of physicians, dentists and veterinarians. The tables listing "Urban-Rural Differences in Physician Supply" and "Type of Practice Distribution" will be of interest to medical students and their advisors.

Other tables of note in the "Cost of Illness" section of the book are those which list "Private and Public Expenditures for Health and Medical Care"; "Estimated Enrollment in Medical Care Insurance and Rate Per 1000 by Type of Insurance"; "Estimated Number of Persons and Per Cent of Population Covered by Voluntary Insurance by States"; "Number of People with Major Medical Expense Protection"; "Number of People with Loss of Income Protection"; "Employee-Benefit Plans"; "Total Costs of Workmen's Compensation" and "Average Annual Number of Physician Visits and Physician Visits Per Person, Per Year by Sex, Age and Place of Visit."

Although the majority of the material is in tabular form, the text on medical organizations, speciality boards, medical finances, regulations and schedules, e.g., narcotics laws, and historical facts is clear, concise and well documented.

This neat compilation of pertinent medical material has resulted in a worthwhile and needed addition to current medical literature.

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